Brain

A Journal of Neurology

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SEPTEMBER, 1940

BRAIN

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SIR HENRY HEAD, M.D., F.R.C.P., F.R.S.

1861 – 1940

Editor of "BRAIN," 1910 – 1925.

"BRAIN" as it has been known to its readers during the past thirty years may truly be said to be the creation of Sir Henry Head, and in its pages which he enriched with his own original papers and edited with such distinction for fifteen years it is fitting that a tribute should be paid to his memory, now that at a ripe age he has passed from the leadership of the English School of Neurology, a school whose traditions he did so much to maintain and to adorn.

This tribute is not alone one of admiration for his genius and for his classical contributions to the physiology of the nervous system and to clinical neurology, but also of warm affection for one who was not only an inspiring teacher but also the very soul of generous encouragement to all those younger neurologists who, during his long and fruitful working life, had the privilege of knowing and of working with him.

Within the limits of this brief memorial notice it would be a presumption to attempt any assessment of that masterly series of related papers in which, with his distinguished collaborators—one of them his successor in the editorial chair of *Brain*, he unfolded the physiology of the sensory nervous system from the study of clinically observed phenomena. Whatever changes the passage of time may have necessitated in this body of work, it has now become an integral and permanent part of neurological knowledge.

Perhaps his later studies on aphasia have yet to receive their due meed of understanding and appreciation. Yet when we come to possess a more complete and coherent psychology and physiology of the speech function, who can doubt that the insight and fine powers of generalization that

always characterized Head's work will be found to have provided a fundamentally important part of their structure.

The following bibliography of his published works is perhaps the most adequate witness to the scientific achievement of Henry Head:—

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AN ANALYSIS OF 1,433 CASES OF PAROXYSMAL TRIGEMINAL NEURALGIA (TRIGEMINAL-TIC) AND THE END-RESULTS OF GASSERIAN ALCOHOL INJECTION

By WILFRED HARRIS.

As I have now had over thirty years' personal experience of alcohol injection in neuralgias, and have seen and treated not less than 2,500 cases of trigeminal tic (1,056 in private practice), in addition to numerous cases of migrainous and other neuralgias, I think that an analysis of my results may be useful in establishing the value and the limitations of this method.

It is now thirty-seven years since Schlösser (1903) published his method of alcohol injection of the main branches of the trigeminal nerve at their deep foramina of exit from the skull, and world-wide experience has shown that it is of value in arresting the painful spasms completely, but not permanently unless the Gasserian ganglion itself is injected. Even now its possibilities are insufficiently understood by the majority of the profession, and it is a commonplace to hear the statement repeated that alcohol injection gives only temporary relief, that it causes facial paralysis, that it is dangerous, and similar disparaging statements. The only ground for such belief is the poor results that will almost certainly follow from injections undertaken by beginners who have not been properly trained in the methods, and it is, I fear, a fact that numerous injections have been made by practitioners who should never have attempted them without previous thorough training and study of the anatomy of the parts.

The duration of the relief with a well placed injection at the foramen ovale will last in the 3rd division for anything from six months to three years in the majority of cases, though occasionally the relief may be complete for as long as ten, fifteen, or as in one of my patients for twenty-three years before recurrence of the neuralgia took place.

The neuralgia mostly affects the 2nd and 3rd trigeminal divisions, but in long-standing cases may spread to the ophthalmic division. It is rare for the 1st or ophthalmic division to be affected alone and it is invariably accompanied sooner or later by spread of the neuralgia into the 2nd division. I have known 1st division neuralgia to continue thus for nine years before spread of the pain to the nose and cheek.

I have suggested previously (1935) the use of the term Trigeminal Tic (T.T.) in place of "Trigeminal Neuralgia," for the reason that there are many varieties of neuralgia affecting the trigeminal area, but trigeminal tic can mean only the paroxysmal form.

The paroxysms of T.T. are especially liable to be provoked by movements of the face, by eating, or by light touches in handling or washing, signs which are most characteristic of the true tic. Yet occasionally cases are met with whose spasms of pain are just as severe and acute but are not started by such movements or handling. I have met with several such, which responded to alcohol injection equally well with the more usual type.

Physiology.— Strong alcohol injected into a bundle of nerve fibres such as the median, instantly coagulates the albumin in the nerve sheath and fibre, setting up degeneration of the nerve fibres to the periphery. Regeneration of the mixed nerve soon commences, new nerve fibres, both motor and sensory, growing downwards from the proximal end of the damaged nerve so that sensation is gradually re-established, and wasted muscles recover, this process being fully completed in about two years. As applied to the 5th or trigeminal nerve, new nerve fibres grow down from the sensory nerve cells in the Gasserian ganglion, whereas the motor fibres take their origin from the motor nucleus within the pons. Nerve cells are also vulnerable to alcohol and destruction of the Gasserian ganglion by alcohol injection will cause total and permanent anæsthesia of the whole trigeminal area, with only temporary motor paresis of the masseter, temporal and pterygoid muscles. These muscles will recover gradually after three months, owing to the fact that though the motor root passing under the ganglion is included in its sheath, yet its trophic cells in the pons are uninjured, and new fibres in time grow down again.

Recent work indicates that the fibres carrying painful and thermal stimuli are minute in size compared with those for tactile impressions. They are not collected into any special bundle between the Gasserian ganglion and the pons, but after entering the latter they pass almost wholly into the descending bulbo-spinal root.

A plea for renaming the 1st and 3rd divisions of the trigeminal nerve. —I have previously suggested (1939) that the 1st and 3rd divisions of the trigeminal nerve should be renamed, the 3rd becoming first, and the ophthalmic division the 3rd division. Developmentally the premaxillary and circumoral area is the most anterior portion of the body, whereas the eye and forehead lie further back. The fibres in the spinal root belonging to the 3rd division or mandibular nerve terminate highest in the bulbo-

spinal nucleus at the mid-medullary level; those of the maxillary nerve or 2nd division terminate below the mandibular portion of the nucleus, whereas the ophthalmic fibres terminate lowest of all, and may be traced as low as the 2nd spinal segment. Thus there would be a continuous segmental succession from the mandibular area (1st division) up the face to the maxillary (2nd division) and then the ophthalmic (3rd division), and so over the top of the head to the 1st and 2nd cervical areas of the occiput, and so to the neck for the 3rd and 4th cervical areas.

Gasserian injection.—The first time I performed injection of the Gasserian ganglion was on November 28, 1910, on a man, aged 43, who had suffered for two years from typical T.T. of the right 2nd and 3rd divisions. The immediate result was total anæsthesia to all forms of sensation including pressure, and loss of taste on the half tongue and palate, diminishing on the following day to light tactile loss and complete analgesia over the whole trigeminal area. This condition persisted unaltered, with diminished taste on the right side, until his death in 1937, twenty-seven years later. There was never any recurrence of neuralgia whatever.

I referred to this case in a paper (1912) I published describing the lateral route of injection of the ganglion. Later in the same year Haertel, (1912), published his method of injection by the anterior route, as a means of producing anæsthesia for surgical operations. It was not until two years later, (1914), that he used it for the treatment of trigeminal neuralgia.

The end-result of a complete ganglion injection may compare exactly with that of a surgical resection of the sensory root behind the ganglion, when the motor root has been successfully spared. Details of the methods of injecting the ganglion are fully given in my book "The Facial Neuralgias" page 48.

Partial Gasserian injection.—Partial injection of the ganglion may also be successfully performed in two ways:—

(1) By destroying the outer portion supplying the 2nd and 3rd divisions of the nerve, causing more or less total permanent anæsthesia of the upper and lower jaws, cheek, inside of mouth and half of the tongue. At the same time partial damage is likely to be caused to the inner portion causing partial analgesia of the ophthalmic division, with moderate preservation of tactile and pressure sense and no risk of keratitis. This result I have found in numerous cases has produced long lasting cure of the neuralgia, from twenty to thirty years, and may be compared with subtotal resection of the sensory root by a neurosurgeon in cases of paroxysmal neuralgia affecting the 2nd and 3rd divisions only. Neither with partial injection nor

in subtotal resection is permanent cure a 100 per cent. certainty, as with both methods recurrence of neuralgia occasionally takes place. For complete certainty of permanent cure either total ganglion injection or total resection of the sensory root is necessary.

(2) A method of injection which I have been using for many years in those rarer cases in which the neuralgia affects the 1st and 2nd divisions, and not the 3rd or mandibular nerve, is to inject only the inner two-thirds of the ganglion with alcohol so as to avoid anæsthetising the tongue and lower jaw. This sparing of the 3rd division may be of great value to the patient, as eating on that side will be less interfered with.

My method of injection of the inner portion of the ganglion is especially valuable also in cases of severe migrainous neuralgia when the attacks of pain are limited to one side and are frequent and crippling. The pain in these cases is around the eye, often in the eyeball or at the back of the eye, and may spread into the cheek and side of nose, but scarcely ever as low as the lower jaw (1940, 1936).

I am not aware whether neurosurgeons ever perform subtotal resections of the sensory root so as to spare only the outer fibres belonging to the 3rd division, but I see no reason why they should not do so.

The best results in these cases will be obtained by a partial ganglion destruction causing complete analgesia of the 1st and 2nd divisions, but without abolishing tactile and pressure sense. This is difficult to obtain as a permanent result, but I have been able to do so in a few cases. The reasons that this is preferable to total anæsthesia of the inner two-thirds of the ganglion are: (1) it is less likely to be followed by causalgic paræsthesia of burning or icy cold sensations; (2) there is less risk of keratitis; and (3) the persistence of tactile sensation in the upper jaw and teeth permits of normal eating on that side afterwards. If the 2nd division has been made totally anæsthetic, eating on that side is interfered with, as owing to the numbness of upper jaw and teeth the patient will prefer to eat on the other side, even though sensation of the lower jaw and tongue is normal. Moreover if the numbness of the inside of the cheek is complete, food is apt to collect there and occasional ulcers may form during the first few months.

The permanent analgesia of the upper two divisions, with little or no tactile loss, resulting from partial injection of the inner portion of the ganglion, may be compared to the results from the tractotomy operation introduced by Sjöqvist three years ago, in which the lower part of the spinal trigeminal root is divided in the mid-medullary region.

Bilateral Trigeminal Tic.—My first bilateral case of T.T. I saw in a Home for

Incurables in October, 1910, a man, aged 31, with complete paraplegia of both arms and legs from advanced disseminated sclerosis, and I injected the foramen ovale on each side at the same sitting, with complete relief of pain, and anæsthesia of both 3rd divisions. Jaw drop, owing to the bilateral motor paresis, caused some difficulty in eating for a few weeks, and a curious initial result was inability to talk for twenty-four hours, owing to the anæsthesia of the tongue temporarily upsetting his articulation.

I have seen a total of 85 bilateral cases, 56 in private practice, a proportion of about 5·3 per cent., or rather over 1 in 20 cases. Since many of these became bilateral several years after I first saw them for a unilateral neuralgia, it may be assumed that 5·3 per cent. is lower than the real figure for bilateral T.T. since it is practically certain that a small further number of my cases, particularly amongst those seen in recent years and not of advanced age, will ultimately develop T.T. on the untreated side. In some the pain may be equally severe on the two sides and may begin about the same time, though in one of my cases, commencing on the left side in 1907, thirty-one years elapsed before the right side became affected. In others the pain on one side may be tolerable and scarcely require injection.

Trigeminal tic and disseminated sclerosis.—Because of the common association of severe shooting pains in tabes dorsalis, one might perhaps expect this to be the form of nervous disease likely to be complicated by T.T., yet I have seen only three cases of tabes with this combination; in two the neuralgia was bilateral.

There seems to be a special liability to trigeminal tic in disseminated sclerosis and occasionally in other forms of chronic spastic paraplegia, as I have met with 39 cases in private practice of trigeminal tic in these diseases, 3 of which were bilateral. Thus disseminated sclerosis or other forms of spastic paraplegia occur in 3·66 per cent. of my 1,056 private cases of T.T. Amongst hospital patients I have notes of 11 cases of T.T. in disseminated sclerosis, 10 in women, 4 being bilateral. Thus of a total of 50 cases of T.T. in disseminated sclerosis, 7 were bilateral, or 14 per cent. The explanation, in my opinion, is that the disseminated patches of sclerosis in the pons and medulla are liable to irritate or render hypersensitive the long spinal trigeminal roots which carry all the pain fibres of these nerves. Any individual whose peripheral nerve-endings in the sinuses or dental nerves have been exposed to sepsis, and who may therefore be said to be vulnerable to T.T., will be therefore more likely to develop it if he, or rather she, has disseminated sclerosis. The greater proportion of bilateral T.T. in disseminated sclerosis cases is also thus accounted for.

That the T.T. complicating disseminated sclerosis is not entirely due to the medullary sclerosis is proved by the fact that these cases of T.T. respond to Gasserian injection or sensory root resection as well as does the usual type of T.T.

The severe paroxysmal trigeminal pain which is sometimes a sequel of the medullary sclerosis following on thrombosis of the posterior inferior cerebellar artery, is quite uninfluenced by Gasserian injection.

Trigeminal tic following trigeminal neuritis.—Neurologists are well aware of the occasional occurrence of numbness of the face and partial trigeminal anæsthesia in disseminated sclerosis, due probably to a patch of sclerosis affecting the entrance of the 5th nerve into the pons, as Oppenheim showed. Such cases in my experience do not develop T.T. later. Less apparent perhaps is the cause of the development of T.T. after trigeminal neuritis. In a paper already referred to (1937), I described three cases in which typical T.T. followed a condition of complete trigeminal anæsthesia of unknown origin. The completeness of the trigeminal anæsthesia, skin, jaws, palate, eye, &c. is strongly suggestive of a sensory root lesion, or possibly of Gasserian ganglion, rather than a diffuse peripheral trigeminal neuritis. So long as the face remained numb, there was no pain, but after the complete disappearance of the anæsthesia, and a varying interval of months or years the T.T. started. I have been unable to suggest the origin of these cases of trigeminal neuritis, but some light has been shed on the influence of neuritis in setting up T.T. by an unpublished case of Mr. Dickson Wright's, in which malignant disease of the floor of the mouth involved the mandible ; the inferior dental nerve in its channel in the bone became exposed to the growth, and it was bathed for some time in purulent secretion. Shortly after, typical T.T. commenced in that area of nerve supply, for which sensory root resection was done. It would appear, therefore, that in certain vulnerable subjects any temporary lesion of the trigeminal trunk or of peripheral trigeminal branches may lead ultimately to the development of T.T. just as in certain persons suffering from disseminated sclerosis the chronic irritation of the medullary sclerotic patches may assist the development of T.T. later.

Clonic facial spasm and T.T.—I have met with 14 cases, 10 women and 4 men, with clonic facial spasm accompanying T.T. on the same side. What the relationship between these two conditions is, I cannot even suggest. Relief of the neuralgia by injection does not stop the spasms, and injection of the facial nerve at the stylomastoid foramen, completely arresting the spasms by producing facial paralysis, has no effect upon the neuralgia, yet the spasms are always on the same side as the neuralgia. These cases

appear to differ completely from three cases published by Harvey Cushing (1920) of Painful Tic Convulsif in which the Gasserian operation failed to relieve the neuralgia, and which were possibly cases of geniculate neuralgia.

Heredity.—I have met with thirty cases of T.T. in which heredity of the disease played a part. In six, or 20 per cent., the neuralgia was bilateral. In a few there was also a history of disseminated sclerosis in a near relative. In one instance a lady had typical T.T. while her son was disabled by disseminated sclerosis, an interesting association in view of the facts I have shown of the close association of these two diseases in about 3·5 per cent. of all cases of T.T. I have treated three members of a family for T.T. in which there had been 11 sufferers from the disease in three generations, 3, 3, and 5.

Emotion, trauma and chill.—Any of these factors may act as the exciting cause of T.T. I have described elsewhere several such cases (1937).

Sex and side affected.—The female suffers nearly twice as often as the male. My total of 1,433 cases (1,056 in private work, and 377 hospital cases of which I have notes) contains 943 women and 490 men, a proportion of 19·26 women to 10 men. Of the bilateral cases the proportion is 32·5 women to 10 men, or nearly twice as often as when unilateral, as is to be expected.

The right side was affected 851 times compared with 497 on the left side, a proportion of rather over 17 to 10. 85 cases were bilateral, and are not included in the proportional figures.

Age of onset.—I have notes of both the age of the patient and the date of first onset of the pain in only 1,119 cases. Of these, 897, or four-fifths, start within the three decades 41 - 70. The largest number, 395, or more than one-third, commence in the decade 51 - 60. Twenty cases commenced under the age of 21, two as early as 12. Eleven cases began after the age of 81, the oldest at 85, whom I injected when aged 87. Quite a large number dated their first attack within two or three weeks of heavy dental extractions, which were not undertaken for neuralgia. Others were edentulous for twenty or thirty years before the first onset of the pain.

TABLE OF AGE ONSET IN DECADES.

12–21	21–30	31–40	41–50	51–60	61–70	71–80	81 and over
20	61	89	235	395	267	41	11

Pathology.—I wish to reiterate here my previously expressed opinion (1926) that peripheral sepsis, such as dental caries, pyorrhœa, antral abscess and sinusitis are the prime causes of the disease.

Septic infection of the dental nerve filaments undoubtedly occurs, and on two occasions I have been able to prove that the bone of the maxilla in edentulous patients with T.T. was crowded with streptococci. It is these peripheral foci of neuritic infection that cause the reflex hypersensitiveness of the cutaneous or gingival branches, the paroxysms being started by other reflex causes, such as movements or handling. It is particularly the two dental bearing branches of the trigeminal nerve which are subject to this type of neuralgic tic, and it is they especially, infinitely more than any other nerve in the body, that are exposed to sepsis throughout life, from the shedding of the milk teeth to the edentulous stage. Perhaps the next more vulnerable spot to sepsis is the tonsil, and the glossopharyngeal nerve that supplies it is the only other nerve besides the trigeminal that is liable to this type of neuralgic tic, though very much less frequently, about 1 glossopharyngeal type to 200 T.T. The distribution of the pain in T.T. is anatomically consistent with the nerve supply, yet no clinical or pathological evidence has been found to indicate any lesion of the nerve trunks or of the Gasserian ganglion. Nerve block by alcohol injection or root resection definitely and immediately arrests the neuralgia, indicating the arrest of painful stimuli passing upwards from the periphery. These facts appear to me to prove the site of the neuralgic foci to be peripheral. The late Wilfred Trotter once told me he agreed with my views. It may be urged that only a very small proportion of sufferers from dental caries develop T.T. On the other hand only a very small proportion of persons exposed to chill develop pneumonia, though the pneumococcus may always be found in the salivary secretions. The particular set of circumstances in each individual must be just right to determine the development of the disease, and the influences of heredity and a special tendency to neuralgia will be accessory factors, e.g. the greater liability to neuralgia in the female. Other factors already referred to occur in disseminated sclerosis and in trigeminal neuritis.

Analysis of Results.

In June, 1939, I commenced a follow-up inquiry of my private cases whose notes indicated good anæsthesia resulting from injections, mostly into the Gasserian ganglion, with relief of pain. 765 letters were thus written, 84 being inquiries to hospital cases, and 457 replies were received from patients or relations, or their doctors. The questionnaire asked for details of recurrence of pain, if any, and as to persistence of numbness, and only those cases whose injection had been done at least three years previously were written to. Of these 457 replies, 316 reported that there had

been no recurrence of pain for a period of three years or more, and the majority of these stated that there had been no alteration in the numbness. Many of my older patients had died during the thirty-two years since I first commenced the injection treatment, but information from near relatives or from their doctor supplied the information required in 48 cases. Thus, a lady, aged 67, a severe sufferer, injected in May, 1909, lived twenty-eight years free of all acute pain, dying at 95. Another woman, aged 77, had bilateral trigeminal tic of both 3rd divisions. Injection of both foramina ovale in October, 1912, produced bilateral anæsthesia with temporary jaw drop and complete loss of pain, with no recurrence for twenty-two years to death at age 99. A doctor, aged 61, injected in October, 1917, for T.T. of left 3rd division, had no recurrence for nineteen years before death in 1936, aged 80.

Amongst those still living, with a record of over 20 years' cure, is a lady, now aged 68, whose neuralgia commenced at age 17 in the right 3rd division. Four years later a surgeon divided the inferior dental nerve, giving two years' relief. The pain then returned as before and continued until I saw her in June, 1909, when aged 37. The first injection failed to hit the nerve at the foramen ovale but a fortnight later on June 28 injection produced total V.3 anæsthesia with complete relief of pain for thirty-one years up to the present time. I had the opportunity of examining her in the late spring of 1940, and found her in good health and spirits with only slight tactile anæsthesia remaining on the lip and chin. This cure may justifiably be called a lucky result, for disappearance of anæsthesia undoubtedly renders the patient liable to a return of the neuralgia, though this does not necessarily recur. Yet I have seen recurrence after twenty-three years' complete freedom in a lady, aged 44, whom I injected in November, 1913, for T.T. of the right 3rd division. There was then, in July, 1936, very little anæsthesia remaining on lip and chin, and I then injected the Gasserian ganglion thoroughly, causing total trigeminal anæsthesia, which persisted, so that her cure should now be permanent.

Further reports include a Major G., now aged 90, who is still well and free of pain twenty-seven years since I injected his Gasserian ganglion in June, 1913, for T.T. of the left 2nd and 3rd divisions. In this case the injection of the ganglion was not complete, being total only of V.3, partial of V.2 and slight only of V.1, yet there has been no recurrence of pain, though he had suffered from the neuralgia for 13 years before I saw him. Another man, aged 36, whom I saw first in June, 1910, had already suffered for 6 years from T.T. of the right 2nd and 3rd divisions. He had had eight injections from another physician with no resulting anæsthesia or relief,

and I gave him four injections between June, 1910, and May, 1912, with relief of eleven months, ten months, and thirteen months. Finally in August, 1913, I injected his Gasserian ganglion, causing total V.3 anæsthesia and partial V.2 and 1. He is still quite well and at work twenty-seven years later, aged 63.

I have accurate notes of all the cases I have treated in my private practice, but of the large numbers I have treated in my two hospitals, St. Mary's and Maida Vale, I have notes of only 367, mostly of cases which for some special reason appeared of interest. Any inferences from my statistics which I shall draw will, therefore, refer mostly to the cases from my private practice.

The 316 who had had no recurrence of pain for three years or more may be divided into the following groups according to length of cure :—

Over 31 years	...	1 case
21–30 years inclusive	...	11 cases
16–20 " "	...	32 "
11–15 " "	...	49 "
6–10 " "	...	118 "
3– 5 " "	...	92 "
		303 cases, plus 13 bilateral

Of the above-mentioned 316 cases, 212 were still alive and completely free of neuralgic tic. They may be divided into similar period groups:

Over 31 years free	...	1 case
21–30 years free	...	9 cases
16–20 " "	...	29 "
11–15 " "	...	31 "
6–10 " "	...	90 "
3– 5 " "	...	52 "
		212 cases

Six of these cases were bilateral and had had both ganglia injected and have been free :—

Right side	Left side	
18 years	16 years	
16 "	14 "	
13 "	6 "	
5 "	5 "	
5 "	5 "	
5 "	4 "	respectively

Herpes.—Patches of shingles of the herpes febrilis type are not an uncommon sequel of Gasserian injection. It occurs around the angle of the mouth, on the lips and chin and ala nasi, and may develop two or three days after the injection. It requires no treatment beyond a little vaseline, and leaves no scars or any subsequent neuralgia such as occurs after herpes zoster.

Loss of taste.—I have notes of the sense of taste being completely lost on the numbed half of tongue and palate in 167 cases. In three cases of bilateral ganglion injection there was complete bilateral ageusia on the front of the tongue. One of these patients, in whom at an interval of several years I had injected the Gasserian ganglion on both sides, had permanent bilateral total trigeminal anæsthesia, and mentioned that though she could taste nothing while food or drink was in her mouth, she could taste at once as soon as she swallowed.

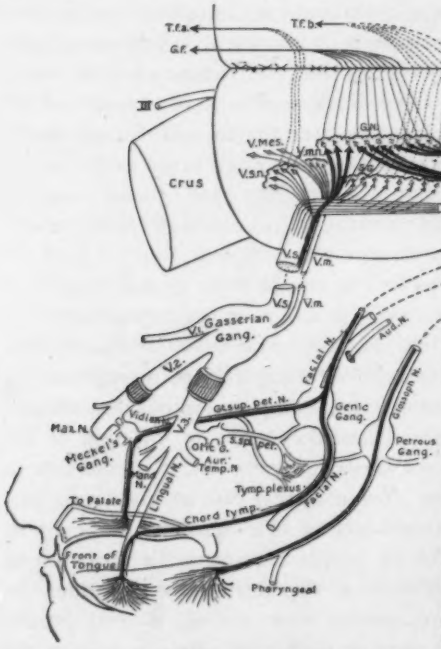
In thirty-four cases I have noted that taste was unaffected although the anæsthesia appeared to be complete. I have not regularly tested this point, even in the majority of my cases, but the results are sufficiently definite to indicate that the gustatory fibres in the chorda tympani and palatal nerves are not always sufficient to carry the stimuli of taste sensation when tactile sense is lost. Sometimes taste is recovered even though the anæsthesia remains complete, but in some of my cases of total ganglion anæsthesia the gustatory loss is still permanent; in one case for over twenty-four years. In two cases the loss of taste was complete over the back of the tongue, pharynx and palate, as well as on the front of the tongue. I have seen this complete loss at least twice in lesions of the trigeminal nerve at the base of the skull. Gowers (1893) has also made the same observation.

Just as in the case of anæsthesia of the tongue from mandibular or Gasserian injection it is very common to find complete loss of taste, temporary or permanent, so also in palatal anæsthesia due to injection of the superior maxillary branch or of the Gasserian ganglion, it is common to find loss of taste on the half palate. Yet in neither case are the actual gustatory fibres damaged. The explanation of this apparent anomaly is, I believe, due to the fact that certain people require tactile sensation to reinforce the gustatory stimuli in order to appreciate taste sensation. In support of this statement I have noticed when testing normal people, that some can at once recognize taste on tongue or palate as soon as the substance is carefully applied, while others cannot recognize any taste at all until permitted to withdraw the tongue and move it about in the mouth.

The anatomical path for the gustatory fibres in the front of tongue is the chorda tympani, thence via the geniculate ganglion and pars intermedia Wrisbergi to the gustatory nucleus of the ascending glossopharyngeal root (fasc.-solitarius). Nageotte showed many years ago that some fibres of the fifth nerve entering the pons terminate in the upper part of the gustatory nucleus. Taste impressions from the pharynx are certainly carried by the glossopharyngeal nerve in the large majority of persons.

Testing taste sensations on the palate is not easy. It is necessary to keep

the tongue gently pressed down by a wide spatula, to avoid the testing material touching the tongue. I use solutions of sugar and of quinine for the tests, painting the liquid on the gently dried tongue or palate with a small camel hair brush. The patient is instructed not to attempt to speak, but to nod the head if taste is perceived, and to point to one of a series of cards marked Sweet, Salt, Bitter, Sour. Heavy smokers I have generally found to be much less acute than non-smokers in perception of taste.



T.f.a.	Trigeminal fillet (tactile and pressure).
T.f.b.	Trigeminal fillet (pain and temperature.
G.F.	Gustatory nucleus.
S.G.	Substantia gelatinosa (nucleus of fifth spinal root.
F.S.	Fasciculus solitarius (ascending glossopharyngeal root).
P.I.W.	Pars intermedia Wrisbergi.
V.m.n.	Fifth motor nucleus.
V.mes.n.	Fifth mesencephalic nucleus.
V.s.n.	Fifth sensory nucleus.
V.sp.	Fifth spinal root.
V.s.	Fifth sensory root.
V.m.	Fifth motor root.

The chorda tympani and great superficial petrosal nerves carrying taste impressions from the front of the tongue and palate respectively are shown uniting in the pars intermedia Wrisbergi. (See "Neuritis and Neuralgia," p. 252.) The glossopharyngeal carries taste impressions from the back of the tongue to the fasciculus solitarius.

Diagram of the course of the Taste Fibres (thick lines) and of the Intra-pontine connections of the Fifth Nerve. (The lower half is represented in profile and the upper in plan. For convenience the gustatory nucleus and substantia gelatinosa are represented in the pons instead of in the medulla).

The path of the taste sensations from the palate is probably via the posterior palatal nerves, Meckel's ganglion, Vidian and great superficial petrosal nerves to the geniculate ganglion, and thence by the pars intermedia to the gustatory nucleus. Thus the geniculate ganglion, through its two main branches, the great superficial petrosal and the chorda tympani nerves, distributes the taste fibres to the buccal cavity, above and below.

Loss of pressure sensibility.—One of the most consistent results of total anæsthesia resulting from Gasserian destruction is complete loss of deep pressure sensibility. This is also found in the anæsthesia of cheek and upper jaw resulting from a successful injection of the maxillary nerve at the foramen rotundum. I demonstrated this point in 1911 at a Neurological Meeting (1911) of the Royal Society of Medicine, and have since pointed it out on many occasions after Gasserian injections. It is essential when testing to support the back of the head firmly, or the patient becomes aware of the pressure on the neck muscles supporting the head. Deep pressure sensibility is therefore a function of the trigeminal and not of the seventh cranial nerve, as has frequently been stated.

Trophic ulceration.—Sores around the ala nasi, especially just inside the nostril, but also sometimes on the cheek or forehead, occur after a small proportion of total Gasserian injections. The nasal ulceration may produce small hæmorrhages, but they are never serious. These trophic ulcerations heal readily if stellate ganglionectomy is performed, and this operation also diminishes the liability to keratitis.

Neuroparalytic keratitis.—Formerly a serious complication after Gasserian operations or injection of the ganglion, I have found the risk of its occurrence much diminished by the regular instillation of a drop of liquid paraffin three or four times daily. If the eye is clean at the time of operation, and lubrication with liquid paraffin, and a protective shade are used for the first few weeks, no trouble will occur in the large majority.

No lint or wool must be used under the shade. Eyes discharging pus from chronic conjunctivitis, or especially if irritated by entropion and incurved eyelashes, or if facial palsy is present, with inability to close the eye, almost certainly will develop keratitis, and if total ophthalmic anæsthesia is necessary to arrest the neuralgia, the lids should be fixed by tarsorrhaphy at the time of the Gasserian operation. Should keratitis develop, the use of atropine ointment ½ per cent. and fomentations bandaged over a smooth piece of oil silk smeared next the eye with atropine vaseline, and regular boracic eye washes, will usually clear up the keratitis. If it should prove too obstinate, closing the lids by tarsorrhaphy for three to six months will always arrest it. When there is a tendency to conjunctivitis, and keratitis is threatening, a useful precaution is to wear spectacles made of a transparent non-inflammable material, such as rhodoid, with a monocular goggle fitted for the affected eye. The side cup is made in one piece with the frame, which can be fitted with any lenses required. Steaming will occur if it be made to fit too closely.

Post-operative hyperæsthesia to cold.—A curious symptom was described by Helson (1932) in Philadelphia who investigated a number of

Frazier's sub-total sensory root resections. He observed in a number of these patients, who were completely anæsthetic to ordinary tests over the maxillary and mandibular areas of the trigeminal area, that they were excessively sensitive to a cold drink, or ice cream, or a cold draught on the numbed side.

I have noted precisely the same phenomenon in a number of my Gasserian injections, with resultant total anæsthesia. It is by no means constantly present as a result of total anæsthesia, indeed it is the exception, but sufficiently frequently met with to prove its reality. It may be due to a lowered threshold of sympathetic sensory conduction. In support of this view I would quote a case of mine (1937), a woman aged 67, who suffered for ten years from T.T. on the left side. In July, 1935, I injected her Gasserian ganglion, producing total anæsthesia to pin, touch and pressure. Three months later she began to suffer from causalgic symptoms of burning pains in the face on the numbed side, "hot pains like a ball of fire, with some darting pain in the left eye." The burning sensations had been getting worse for the last six weeks, though tests showed that the anæsthesia was still unchanged and total to pin and pressure. She complained that she could not sit with her left face exposed to the heat of a fire, which aggravated her sensations of burning. Testing the cheek with a hot test tube pressed against it for 20 seconds produced no sensation of heat, though a blister was raised and a flush produced. I then tested her by exposing the left face to an electric radiator, shielding the head and neck by a piece of cardboard, with a window cut in it to allow the rays to impinge on the left cheek and forehead only. Repeated tests with her eyes shut proved conclusively that she felt the heat of the radiator as soon as an intervening piece of card was moved away. I then did a stellate novocain test, injecting 10 c.c. 1 per cent. novocain around the stellate ganglion on the neck of the first rib (1936). This produced a typical Horner syndrome and warm flushed hand and forearm, and testing again with the cardboard shield she felt the heat indefinitely, and much slower in perception, and no burning pain when the cheek was exposed to the radiator, but for about eight hours she was entirely free of the burning causalgic pains. I therefore got Mr. Dickson Wright to do stellate ganglionectomy. For several weeks the spontaneous burning pains were improved, but ultimately returned.

Post-operative trigeminal causalgia. Atypical neuralgia.—In a small proportion of Gasserian operations or injections, although the true tic may be entirely cured and the trigeminal anæsthesia complete, yet a new type of pain may appear in from six weeks to three months afterwards. The term trigeminal causalgia may be justified by the frequency of com-

plaint of burning sensations in the face. This is not a paroxysmal violent spasm, but is constant and is described as a "drawing," surging type of pain, often burning in the cheek and around the eye, and accompanied by slight shoots of pain in or around the eye and towards the ear. It is much commoner in the female, men very rarely suffering in this way. Further Gasserian injection or operation is of no avail, indeed further injections usually make the pain apparently worse. Nor is stellate ganglionectomy of any value in such cases. The pathology of these post-operative pains is obscure. Functional neurosis is probably partly accountable, at any rate in some cases. The resemblance of the pains to the well-known causalgia of median or internal popliteal gunshot wounds is distinct, and it is possible that the pains are central in origin due to spontaneous release either in the bulbo-spinal trigeminal nucleus in the pons and medulla, or else higher up in the thalamus. If the pains arise in the medullary nucleus then resection of the trigeminal fillet on the opposite side in the pons might give relief. This operation has already been performed a few times.

This post-operative trigeminal causalgia seems to me to be identical with Frazier and Russell's (1924) atypical neuralgia which may arise spontaneously in untreated cases.

Many names have been given to this type of pain. In 1926 I described it as chronic neuralgia of the jaws (1926), and in America Mark Glaser (1928, 1938, 1940) has written several papers on it under the title Atypical Neuralgia. He well describes the pain as constant, drawing, burning, pressing, but at the same time he includes migrainous neuralgia in the symptom complex. This latter syndrome which I have described (1936) differs notably from the trigeminal causalgias and primary atypical neuralgia of Frazier and Russell in being intermittent, and in affecting men nearly as often as women. Further, in my experience, migrainous neuralgia may often be cured completely by Gasserian injection (1940), which is usually useless in the treatment of what has been described as atypical neuralgia. Frazier and Russell gave the syndrome this name because it differs from the typical paroxysmal trigeminal tic. It is, however, an unsatisfactory term and is liable to be used for including many irregular forms.

Alajouanine and Thurel (1933) described the syndrome as Sympathalgies Faciales and other writers also have suggested a role of the sympathetic system in their causation.

The possibility of the sympathetic system being the afferent path for these sensations I have discussed elsewhere (1936) and also earlier in this paper.

SUMMARY.

1,433 cases of trigeminal tic have been analysed to show relative sex frequency, the average age of onset of the disease, the proportion of bilateral cases, and the association of the disease with disseminated sclerosis, trigeminal neuritis and clonic facial spasm. Evidence is given in support of my view of the pathology of the disease, that a septic peripheral neuritis of dental or sinus origin is the prime cause. Gasserian injection, both partial and complete, is described, and compared with injection of the nerve branches and with sensory root resection. 316 cases of Gasserian injection whose cure had lasted three years or more are analysed according to periods of immunity, and 212 of these who were still alive at the time of writing are similarly divided. Additional effects of total Gasserian injection discussed are (1) Herpes, (2) loss of taste, (3) loss of pressure sensibility, (4) trophic ulceration, (5) keratitis, (6) post-operative hyperæsthesia to cold, and (7) post-operative facial causalgia.

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OPTIC ATROPHY ASSOCIATED WITH PERNICIOUS ANÆMIA.

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It has been known for many years that failure of vision may occur in the later stages of pernicious anæmia when hæmorrhages into the retina involve the macula (Gowers, 1890), but it is only recently that optic atrophy occurring early in the course of the disease has been recognized. The type of disturbance of the visual fields in these cases has received little attention. Three cases of visual failure due to optic atrophy occurring as an early symptom of pernicious anæmia have been under treatment recently at the National Hospital, and it has seemed worth while to record them in order to emphasize their distinctive features.

Survey of Previous Literature.

In the early literature there are a few records of the occurrence of optic atrophy in cases of subacute combined degeneration of the cord. Bastianelli (1897) referred to a man with anæmia and a spastic paraplegia who developed atrophy of the optic nerves which was confirmed by post-mortem examination, but no further details of the onset of the visual disturbance are mentioned. Byrom Bramwell (1910) recorded an unusual case of a man aged 33 who had a history of a relapsing ataxic paraplegia with sphincter disturbance, and developed failure of vision and pallor of the optic discs. The case clinically seemed a typical one of disseminated sclerosis, but shortly before death he developed severe pernicious anæmia from which he died. The post-mortem examination showed the typical changes of subacute combined degeneration and pernicious anæmia, but no pathological examination of the optic nerves is mentioned.

Bickel (1914) recorded a case of gradually progressive spastic ataxia, in which a central scotoma developed in the left eye. The fundus remained normal. At post-mortem examination degeneration in the postero-lateral columns of the cord and in the medulla oblongata were found and these were attributed to funicular myelitis. Both optic nerves showed areas of degeneration, in the left nerve near the centre where it involved the papillo-macular bundle, and in the right nerve nearer the periphery. The case

appeared to be one of subacute combined degeneration, though there was little evidence of pernicious anæmia.

Woltmann (1919) referred briefly to a case of pernicious anæmia with transverse myelitis and a scotoma in one eye, but he was doubtful of the ætiology of the neurological symptoms and was inclined to attribute them to syphilis.

An isolated case of bilateral optic atrophy with severe failure of vision, associated with pernicious anæmia and a flaccid paraplegia with extensor plantar responses was reported by Dereux (1929). This author commented on the rarity of optic atrophy in cases of pernicious anæmia.

Young (1932) briefly mentioned one case with optic atrophy in a large series of cases of pernicious anæmia.

Cohen (1936) was the first to call attention to the fact that visual failure might be the presenting symptom in pernicious anæmia, and that this might occur when there were only slight changes in the blood-picture and no other evidence of disease in the central nervous system. He recorded two cases of this type which responded to liver therapy with practically complete recovery of vision.

Since then a few further cases have been recorded, in some of which visual failure was a presenting symptom, while in others it developed later in the course of the disease (Box, 1936; Talbot, 1936; Kampmeier and Jones, 1938; and Courville and Nielsen, 1938).

A remarkable case was recorded by Guillain, Lerebouillet and Auzepy (1938) of a woman, aged 64, who developed external ophthalmoplegia, weakness of the muscles supplied by the 5th cranial nerve, and bilateral primary optic atrophy with considerable reduction of visual acuity. After the patient had been under observation for two years unmistakable signs of anæmia appeared and a blood count showed that she had a severe macrocytic anæmia, there was also absence of acid in the gastric juice. The anæmia responded satisfactorily to liver therapy, but there was little change in the visual acuity or cranial nerve palsies. The authors considered that the neurological signs in this case were directly associated with pernicious anæmia.

Illustrative Cases.

Case 1.—H. M., a man, aged 46, was admitted to the National Hospital under the care of Dr. Gordon Holmes on March 29, 1938, complaining of "difficulty in seeing."

His history was that for twelve months his vision had been gradually failing; at first figures looked blurred and he had difficulty in reading small print, but by the time of admission his vision was so poor that he was unable to read ordinary newspaper print and could only read the headlines. He had some difficulty in

recognizing people in the street, but he could still distinguish colours For the whole period the vision in his left eye had been worse than in his right eye

For six months also his legs had felt heavy and had gradually become weaker, and at times he staggered when he walked. There was no numbness or tingling in the hands or feet. He had become impotent during the previous few months. There had been no soreness of the tongue, and he had felt fairly well in himself.

His past history was uneventful ; he was a teetotaller, and he smoked about fifteen cigarettes a day, but no pipe tobacco.

On examination his hair was thin and greyish, and there was a suggestion of a yellow tint in the conjunctivæ. His mucous membranes were definitely paler than normal. His tongue had a normal surface and there was no atrophy of the papillæ.

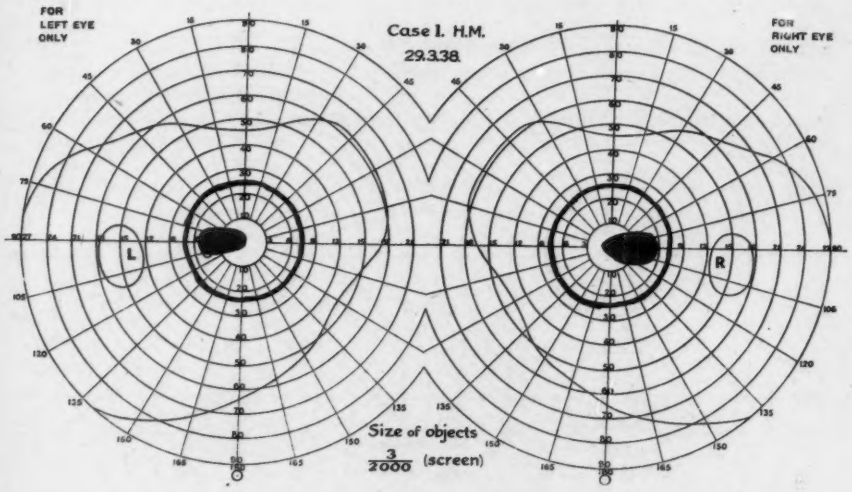

FIG. 1.

Neurological examination.—V. A. R. $\frac{6}{24}$ and V. A. L. $\frac{6}{36}$ (corrected). There was slight but definite pallor on the temporal sides of both optic discs.

The visual fields on perimetry were full to a 3 mm. object. Examination of the central fields showed bilateral centro-cæcal scotomata which were oblong in shape, with the fixation point just included at the inner end of the scotoma.

The pupils were medium-sized and reacted normally to light and on convergence, and the other cranial nerves were normal.

In the arms tone, power and co-ordination were normal, but in the legs there was slight extensor spasticity with moderate diminution of power, and ataxia in the heel-to-knee test.

The arm jerks were normal, but the knee and ankle-jerks were greatly increased, and there was a bilateral extensor plantar response. The upper abdominal reflexes were weak and the lower ones were absent.

On examination of sensation there was some peripheral impairment to light touch on the legs, but otherwise cutaneous sensation was normal. Position sense was normal in the fingers, but was deficient in the toes. Appreciation of vibration was impaired on the iliac crests and was absent on the malleoli.

The blood-count was Hb. 71 per cent.; R.B.C. 2,900,000 with colour-index of 1·2; W.B.C. 5,600 with 65 per cent. of polymorphs ; 34 per cent. lymphocytes; and 1 per cent. of large mononuclears.

An alcohol test meal showed absence of free HCl after injection of histamine.

A diagnosis of pernicious anæmia was made and he was treated with injections of Anahæmin, at first 2 c.c. daily, and later 2 c.c. three times a week ; he was also given pil. ferri gr. 30 three times a day.

His blood-count improved rapidly and on discharge from hospital four weeks later his Hb. was 88 per cent. and R.B.C. 4,780,000 with a colour-index of 0·92. There had been moderate improvement in his vision so that he was able to read ordinary newspaper print. V.A.R. was $\frac{6}{18}$ and V.A.L. $\frac{6}{36}$, and there was little change in the visual fields.

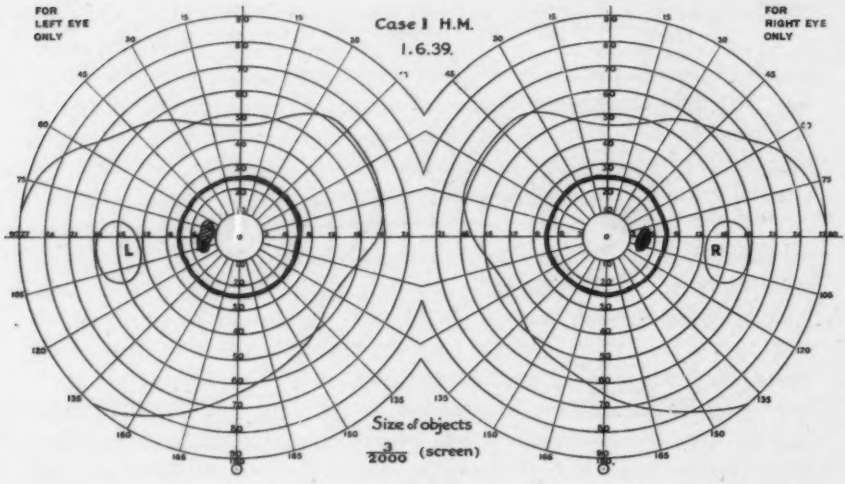

FIG. 2.

He was re-examined on June 1, 1939. In the interval he had been receiving injections of Campolon twice a week. He had improved steadily and felt very well in himself. His vision had gradually improved and he was able to read everything except the smallest print ; he stated that he could read a motor number plate at forty yards. He continued to smoke about ten cigarettes a day.

On examination his vision was V.A.R. $\frac{6}{6}$ (partial) and V.A.L. $\frac{6}{6}$ (corrected). There was slight temporal pallor of the optic discs, more marked on the right than on the left.

The fields were charted and showed full peripheral fields to a 3 mm. object. The central field was normal on the left, and on the right there was a small relative paracentral scotoma to a 3 mm object.

The knee and ankle jerks remained brisk and the plantar reflexes extensor ; appreciation of vibration remained absent at the ankles.

The blood count was Hb. 105 per cent. and R.B.C. 5,160,000 with a colour-index of 1·0.

Case 2.—B. B., a man, aged 52, was admitted to the National Hospital under the care of Dr. Gordon Holmes on April 24, 1939, complaining of progressive failure of vision.

The patient was a keen fencer, and twelve months before admission he found that he was losing all his fights because he was misdirecting his weapon. He consulted an eye specialist because of this and his vision at that time was passed as normal. Shortly afterwards he noticed that when he closed his left eye, the sight in his right eye was poor, and during the following nine or ten months the vision in the right eye progressively became worse.

Two months before admission he entered a clinic at Copenhagen for investigation of the failure of vision. X-rays of the skull showed no abnormality, Wassermann reaction was negative and a lumbar puncture showed no increase of pressure; the cerebrospinal fluid was normal. No definite diagnosis was made and he returned to England.

Two weeks before entering hospital he noticed that the vision in his left eye was not as good as it had been previously, and there was some further impairment of vision in the next fortnight.

There were no other symptoms except for some difficulty in concentration during the previous three weeks.

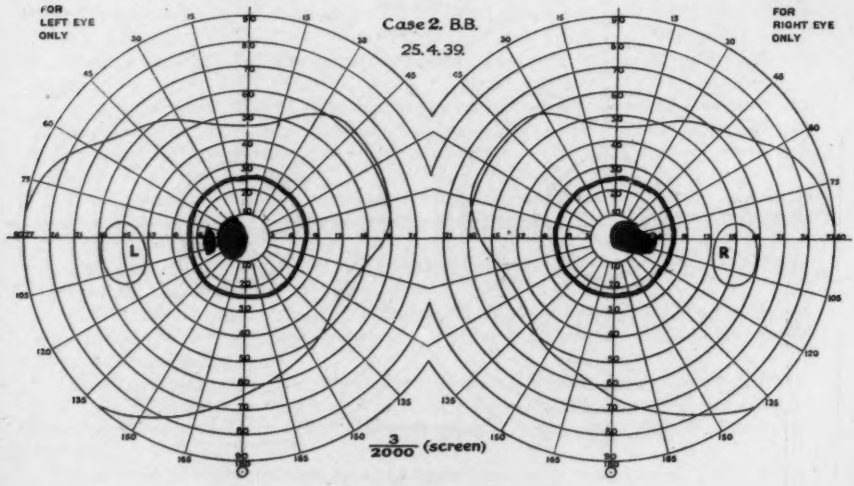

FIG. 3.

His past history was uneventful, except for an operation on the fontal sinuses seven years previously, after which he had lost his sense of smell. He was a fairly heavy smoker, both of cigarettes and of pipe tobacco.

On examination his skin had a yellowish tint, with increased redness over the malar bones. The mucous membranes were slightly pale, and the tongue was furred; there was some atrophy of the papillæ. No abnormality was found in the heart, lungs, or abdomen.

Neurological examination.—There was bilateral anosmia. V.A.R. $\frac{6}{6}$ and V.A.L. $\frac{6}{24}$ (partial) (corrected). There was slight generalized pallor of the right optic disc, with clear-cut edges, while the left optic disc was within normal limits.

The visual fields on perimetry showed slight general constriction to a 3 mm. object. In the central fields there was an oblong centro-cæcal scotoma in the right eye, which was absolute and had clear-cut edges, while in the left eye there was an absolute scotoma which involved the fixation spot on its medial side but stopped just short of the blind spot laterally.

The pupils were fairly small, and the reaction of the right one to light was more sluggish than normal, while the reaction of the left one was normal. The other cranial nerves were normal.

Tone, power and co-ordination were normal in the arms and legs. The arm-jerks were normal, the knee-jerks sluggish and the ankle-jerks absent. The abdominal reflexes were normal and the plantar responses flexor.

The only abnormality of sensation was marked impairment of appreciation of vibration on the malleoli.

The blood count was Hb. 86 per cent.; R.B.C. 4,260,000, with a colour index of 1·2; the halometer reading was 7·9 μ; W.B.C. 5,600. A Price-Jones curve was plotted and this showed a shift to the right with some spreading out of the curve. The mean diameter was 8·05 μ with a standard deviation of 0·63 μ and a co-efficient of variation of 7·8 per cent.

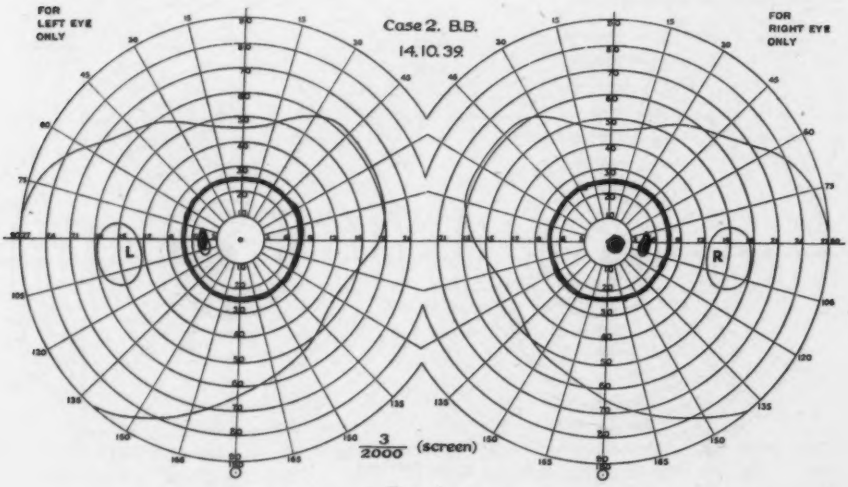

FIG. 4.

There was no free HCl in the gastric juice after histamine injection.

A diagnosis of pernicious anæmia was made and the patient was treated with injections of 4 c.c. of Campolon daily, which was reduced after three weeks to 4 c.c. on alternate days. He also was given ferrous sulphate, gr. 6, three times a day.

There was improvement in the blood count and in his sense of well-being, also gradual improvement of vision.

On discharge after five weeks of treatment the Hb. was 100 per cent.; R.B.C. 4,340,000 and colour index 1·15. V.A.R. was $\frac{6}{36}$ and V.A.L $\frac{6}{9}$. The scotoma in the right eye was only slightly smaller, but there was considerable improvement in the left eye where the absolute scotoma had been replaced by a relative one in which there was hazy vision.

On October 14, 1939, that is nearly six months after treatment had been started, he was examined and vision was found to have improved considerably, V.A.R. was $\frac{6}{18}$ (partial) and V.A.L. $\frac{6}{6}$ (partial) (corrected). On testing with a 3 mm. object on the Bjerrum screen no scotoma could be demonstrated in the left eye and there had been marked reduction in size of the scotoma in the right eye.

Case 3.—R. D., a clergyman, aged 57, was admitted to the National Hospital under the care of Dr. Gordon Holmes on May 22, 1934, complaining of failing vision.

Eighteen months before, following an attack of influenza, he had become more easily tired than previously. Six months later he noticed that he had difficulty in seeing small print when he was reading; this seemed to him to be due to patches of mist in front of his eyes. His vision gradually became worse during the next six months, and he had been unable to read during the six months before admission.

Eight months before, his legs had become stiff and weak, and this had gradually increased, so that he had difficulty in walking. There had also been numbness in the hands and feet for two or three months.

His previous history was uneventful, except that he was rather a heavy smoker.

On examination the mucous membranes were rather pale, and the tongue showed some atrophy of the papillæ. The heart, lungs and abdomen were normal.

Neurological examination.—V.A.R. was $\frac{6}{60}$, and V.A.L. $\frac{2}{60}$ (corrected). Both optic discs were pale, chiefly on the temporal sides, the left being paler than the right.

The visual fields showed moderate peripheral constriction and the central fields large paracentral scotomata involving the blind spots. The pupils reacted briskly to light, but the constriction was poorly maintained. The other cranial nerves were normal.

Tone, power and co-ordination were normal in the arms, but in the legs there was some increase of extensor tone with considerable weakness and unsteadiness in the heel-to-knee test.

The arm-jerks were normal, the knee-jerks sluggish and the ankle-jerks absent. The plantar responses were extensor.

There was no impairment of cutaneous sensation, but sense of position was impaired in the toes, and appreciation of vibration was absent on the legs and pelvis, though normal in the arms.

The blood-count was Hb. 56 per cent.; R.B.C. 2,550,000 with a colour index of 1·09; the halometer reading was 8·1μ; W.B.C. was 4,000 with 54·5 per cent. of polymorphs and 45·5 per cent. of lymphocytes. A test meal showed absence of free HCl.

Treatment of the pernicious anæmia was started with injections of 2 c.c. Campolon daily, together with ferri et ammon. cit. gr. 30 three times a day. Three weeks later on discharge he was feeling better and was walking more easily, but there had been little change in his vision. Hb. was 73 per cent. and R.B.C. 3,840,000 with a colour index of 0·95.

In answer to a letter on May 29, 1939, he stated that he had been taking stomach extract and iron regularly since discharge from hospital. He was feeling well, except for slight stiffness of the legs, and he was able to do his work as a clergyman normally. His vision had gradually improved since leaving hospital, and, though it was not quite as good as before his illness, he was able to read well except very small print. He was able to read a car's number plate at twenty-five yards.

Owing to the distance from London, at which he lived, it was impracticable to examine him again.

Frequency of Optic Atrophy in Pernicious Anæmia.

It is difficult to estimate the frequency of the occurrence of optic atrophy in cases of pernicious anæmia, and this small series of three cases cannot help on that point. Judging from the figures given in papers, recording large series of cases of pernicious anæmia it must be rare. Woltmann (1919) found one doubtful case amongst 150 cases of pernicious anæmia; Young (1932) found two cases amongst 515 patients with pernicious anæmia studied at the Brigham Hospital, while Smithburn and Zerfas (1931) do not mention optic atrophy as occurring amongst 115 cases. All these authors were studying the neurological symptoms. Castle and Minot (1936), in discussing the symptomatology of pernicious anæmia state that defects of the special senses are rare, the commonest being "optic atrophy and optic neuritis." They emphasize, however, that defects of sight are fairly common, but are usually dependent upon severe anæmia or retinal hæmorrhages.

Stage of Disease at which Optic Atrophy may Occur.

As Cohen (1936) emphasized, impairment of vision resulting from optic atrophy may be the earliest symptom of pernicious anæmia, and on examination there may be little evidence of anæmia and none of sub-acute combined degeneration of the cord. In my first two cases visual failure was the first symptom of which the patient complained, while in the third case general fatigue preceded visual failure by six months. In some of the other reported cases visual symptoms have appeared when the symptoms of anæmia are obvious and when there has been widespread evidence of changes in the spinal cord.

The onset of visual failure does not depend directly on the degree of anæmia, as in one of Cohen's patients the hæmoglobin was 94 per cent. when the vision had already fallen to $\frac{6}{60}$ and there was marked pallor of the optic discs, and in my second case the hæmoglobin was 86 per cent. one year after progressive visual failure had been noticed. In many cases of pernicious anæmia there is no visual impairment in spite of low hæmoglobin values.

Characteristics of Visual Failure.

In my three cases visual impairment had been slowly and steadily progressive and this seems to have been the course also in most of the recorded cases. In Box's (1936) patient there was a fairly sudden failure of vision, especially in the right eye, but as there was a macular hæmorrhage in this eye it is likely that this accounted for the more rapid failure.

In the early stages there is little alteration in the colour of the discs, but as the disease progresses primary optic atrophy appears. The response of the pupils to light seems to depend on the degree of vision remaining; when vision has become markedly impaired the pupillary reaction becomes sluggish.

Type of Field Defect Produced.

Bickel (1914) mentions that there was a central scotoma in one eye of his patient and Talbot's (1936) patient had central scotomata in both eyes. Cohen's (1936) patients both had slight peripheral constriction of the fields and Courville and Nielsen's (1938) patient had gross peripheral constriction, but in the other reported cases no definite mention is made of the type of field changes.

In the three cases here recorded the peripheral fields have been charted on a perimeter and the central fields have been studied on a Bjerrum screen at a distance of 2 metres. In the peripheral fields only slight general constriction has been found with no sector defects. The important changes have been limited to the central fields; in two of the cases there have been central scotomata either involving the blind spot or stopping just short of it. A characteristic feature of these scotomata is that they have been oblong with the fixation point at one end of the scotoma, and have not been pericentral with the fixation point in the centre of the scotoma; the edges of the scotomata have been fairly sharp. The third case showed large paracentral scotomata including the blind spot in the scotoma.

Differential Diagnosis.

Tabetic optic atrophy has been the provisional diagnosis made in a few of the reported cases. There are certain features in the visual fields which should distinguish the two conditions. In tabetic optic atrophy the field defect consists of two main features (Traquair, 1938), a general depression of vision which is fairly equally distributed over the whole field, and localized depressions of vision which may be sharply limited from the rest of the field but which occur in the periphery. These changes are not seen in the cases under discussion where there is a scotoma, a finding of extreme rarity in tabes dorsalis. Paton (1922) and Traquair (1938) say that they have never seen a scotoma in tabes dorsalis; Uhthoff (1915) reproduces a chart of a case of tabetic optic atrophy with bilateral pericentral scotomata, but in this patient there was also considerable constriction of part of the peripheral field in one eye.

In tabetic atrophy the pupillary reaction to light is always lost, while it remains brisk till the vision is considerably reduced in the cases of pernicious anæmia.

Compression of the optic chiasma may rarely cause bilateral central scotomata without changes in the peripheral fields (Cushing, 1930); this may occur with compression from above, especially by craniopharyngiomata, but it may occur also in a small percentage of pituitary adenomata; Henderson (1939) found this type of defect in six cases out of a series of 338 from Cushing's clinic. This type of case can usually be distinguished by X-rays of the skull.

The most difficult differential diagnosis is from sporadic cases of Leber's disease occurring late in life, and from tobacco amblyopia. In Leber's disease the scotomata are usually pericentral rather than of the type described here, but in tobacco amblyopia the common type of field defect is an oblong centro-cæcal scotoma, and in both these diseases the peripheral fields are usually unaltered. It would seem to be advisable to examine the blood and gastric secretions for evidence of pernicious anæmia in patients where either of these conditions is suspected, and also in the group of cases of bilateral optic atrophy occurring in middle life for which no adequate cause can be found.

Treatment and Prognosis.

If cases of pernicious anæmia with optic atrophy are treated early and thoroughly with liver injections the prognosis regarding return of vision is good. In four of the recorded cases in which liver therapy has been given vision has continued to fail or has remained stationary in spite of treatment, but in two of these cases (Young, 1932, and Guillain *et al.*, 1938) the patient was practically blind before treatment was started and in a third one (Kampmeier and Jones, 1938) there was considerable visual failure by the time that the diagnosis had been made, and as the case was seen in 1927 treatment consisted of a liver diet and the blood count did not return to normal. The only apparent exception is Talbot's (1936) case in which vision continued to fail in spite of what were regarded as adequate injections of liver, but when the blood counts are studied it will be seen that the dosage must have been inadequate, as the red cell count fell steadily while vision was failing.

The return of vision under treatment is usually slow and may not be quite complete, but the prospect of return of useful vision is good in a patient who is treated thoroughly before atrophy is advanced.

Pathology.

The only available post-mortem study of the optic nerves in a case of this type is reported by Bickel (1914), when areas of degeneration were found in both nerves, although visual impairment had been confined to one eye. In these areas there was considerable proliferation of the neuroglia and round-cell infiltration of the tissues and around the blood-vessels. A condition with a close resemblance to the human disease has been found occurring spontaneously in cage monkeys by Scherer (1937); these animals have developed changes in the spinal cord which closely resemble those found in human subacute combined degeneration, and in many of the affected animals areas of degeneration have been found in the optic nerves. Later work (Scherer, 1939) has shown that these areas affect particularly the part of the optic nerve occupied by the papillomacular bundle.

The exact pathology in early cases of visual failure must remain a matter of speculation, but presumably there is a process similar to that in the spinal cord in subacute combined degeneration which is reversible when adequate treatment is given; if, however, treatment is started too late or is inadequate, complete degeneration of the nerve fibres appears to take place, as judged by the colour of the optic discs and the degree of loss of vision (Dereux, 1929, and Kampmeier and Jones, 1938, third case).

The cause of the optic atrophy is deficiency of some factor present in liver, but whether this is the same factor of which the absence is responsible for the degeneration in the spinal cord and peripheral nerves in subacute combined degeneration it is not possible to say.

Summary.

Three cases of visual failure occurring early in the course of pernicious anæmia have been described.

The clinical features of these and previously reported cases have been reviewed and the good prognosis, if adequate treatment is given in the early stages, has been emphasized.

I wish to thank Dr. Gordon Holmes for his permission to publish these cases, which were under his care, and for his help in the preparation of this paper.

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A FORM OF FAMILIAL PRESENILE DEMENTIA WITH SPASTIC PARALYSIS

(INCLUDING THE PATHOLOGICAL EXAMINATION OF A CASE).

BY C. WORSTER-DROUGHT, J. G. GREENFIELD AND W. H. McMENEMEY.

CERTAIN forms of presenile dementia are known to exhibit an hereditary or familial incidence. In addition to Huntington's chorea, the transmission of which through many generations is well known, both Alzheimer's and Pick's diseases may show a familial incidence. Familial examples of Alzheimer's disease have been described by Lowenberg and Waggoner (1934) and by McMenemey, Worster-Drought, Flind and Williams (1939). Undoubted cases of Pick's disease showing a familial incidence have been recorded by Grünthal (1926 and 1930), Verhaart (1930), Schmitz and Meyer (1933) and Braunmühl and Leonhard (1934), while in several other examples of this disease a history of unspecified mental disorder in relatives of the patient has been recorded.

In 1933, under the heading of "Familial Presenile Dementia with Spastic Paralysis" two of us described a case showing an unusual combination of dementia and spastic paralysis. A sister of this patient was regarded as showing early signs of the same disorder and from the history obtained it was apparent that eight other members of the family, spread over three generations, had been similarly affected. Since the publication of our paper in 1933 the first of our two patients has died and we have been able to carry out an histopathological examination of the nervous system. As a result of (1) the unusual pathological findings in this case, and (2) the fact that our second case, now under observation for seven years, has progressed in exactly the same manner as the first, we are presenting this further report.

CLINICAL DESCRIPTIONS.

Case 1 (*C. G., No.* 29 *in the family tree*).—This male patient was under observation from 1929, a year after the onset of symptoms, until his death in 1936 at the age of 54. As a full description of the clinical features up to 1933 was given in our original paper, it is necessary only to summarize the particulars of the case up to that date.

Charles G., an engine driver, was first seen on June 14, 1929, at the age of 47, complaining of "difficulty in speaking, lack of interest in his affairs, and defective

memory." The first symptoms of indistinct speech had developed slowly over a period of a year while the other symptoms had appeared more recently. It had also been noticed that he was becoming careless at his work. He had had no previous illnesses of importance.

When examined in 1929 his speech was indistinct and slurred. There was some slight increase of tone in the lower limbs and right arm and the right knee and ankle jerks were "brisker" than the left; there were no other abnormal signs in the central nervous system. The gait at that time was normal and there were no tremors. Cardiovascular, respiratory and renal systems were normal. The resting pulse-rate was 80 and the blood-pressure 155 systolic, 90 diastolic.

By June, 1930, there was no material change excepting that the gait had become more deliberate and careful. He was kept under observation as an out-patient and towards the end of 1932 was admitted to hospital. An examination at this time revealed the following state:—

Mental state.—His mood was complacent; throughout the day he remained inert, sitting for hours looking into space and making no attempt to occupy himself in any way beyond smoking. His speech was scanty, slurred and indistinct. Attention was good but there was usually a delay in answering questions and sometimes he made no reply. His answers were invariably brief and there was complete absence of spontaneous speech although when engaged in conversation he confabulated readily. He was able to repeat a question after one or two minutes and when asked the cause of the delay would say "I was dreaming." In answer to the question "What do you do to occupy yourself during the day?" he stated that he read the *Daily Herald* when in fact he never attempted to read at all. He had no idea how long he had been in hospital; when asked, he would say that he came in "last night" when, indeed, he had been in for several weeks. He did not know the date or even the month. His remote memory was good, e.g. he stated correctly that he had entered the S.E. & C. Railway Service at the age of 13; he gave correctly the dates of the beginning of the Great War and of the Armistice; he also knew the name of his school and the age at which he left. He appeared to understand all questions readily but had no memory of recent events, e.g. he did not know when his wife last came to see him. When up, he went regularly to the lavatory but when in bed was incontinent. He was quite devoid of insight and retention tests showed great impairment. Hallucinations were not evident.

Physical examination.—The pupils were equal, central and circular; they reacted somewhat sluggishly to light but normally on accommodation. The optic discs were normal, the vessels showing slight arteriosclerosis. Speech was hesitant and slurred with over-action of the facial muscles and a slight tremor of the tongue. Sensation was apparently normal to all forms of stimuli. Power in the upper limbs was good but muscular tone was increased in both arms and all tendon reflexes were exaggerated. The gait was slow, deliberate and somewhat spastic on a widened base. The muscular tone of the legs was much increased, more so on the right than on the left. The knee and ankle jerks were exaggerated but about equal. There was no ankle clonus. The plantar reflexes were flexor and the abdominal reflexes absent. No tremor was present in the limbs. Co-ordination of the arms was fairly good but there was slight swaying in the Romberg position.

The radial and dorsalis pedis arteries were only slightly thickened. The pulse-rate was regular (76) and the blood-pressure 140/90. The liver was impalpable. The blood Wassermann reaction was negative on three occasions during the last three years. Cerebrospinal fluid: two small lymphocytes per c.mm.; total protein 50 mgm. per cent.; Pandy reaction very faintly positive; Wassermann and Lange reactions negative.

Progress subsequent to 1933.—The patient was afterwards transferred to a private home where he remained for three months. During this period his mental condition and conduct gradually deteriorated. At times, he was confused and irritable with an inclination to throw things about. In February, 1934, he was admitted to the National Hospital, Queen Square, under the care of Dr. Macdonald Critchley, the dementia and ataxia having progressed during the interval. On March 19, 1934, the case was shown before the Neurological Section of the Royal Society of Medicine by Dr. Graeme Robertson. Mentally, the patient showed complete confusion and disorientation with perseveration and confabulation. Emotional reactions were absent. His speech was practically monosyllabic with gross slurring. He could still feed himself but apart from this he showed no spontaneous activity. Dr. Robertson had observed that he used his right hand more freely and, to command, more accurately than his left. Also, the arms were inclined to show restless movements of a vague exploratory character; this was more pronounced in the left hand which although not exhibiting a definite grasp reflex, frequently included the fingers of his other hand or the bedclothes. The arms remained about the same as previously but the legs were now maintained rigidly in extension with pronounced resistance to passive movements in any direction and especially to flexion.

All deep reflexes continued to be extremely brisk; he now showed bilateral ankle clonus but the plantar reflexes remained flexor. The gait was uncertain and unsteady. The pupils, optic discs and other cranial nerves remained normal. At the National Hospital, examination of the cerebrospinal fluid showed an increase in the total protein to 110 mgm. per cent. but no other abnormality.

In May, 1934, the patient was admitted to Tooting Bec Mental Hospital, and we are indebted to Dr. P. M. Turnbull, Medical Superintendent, for allowing one of us (C. W.-D.) facilities for examining him there on different occasions and subsequently for the pathological material.

On examination in August, 1935, C. G. was found completely demented, making no attempt at speech beyond the one word "fine," which was uttered in reply to all questions and commands. He would purse his lips frequently and occasionally protrude his tongue. He could not walk, was doubly incontinent, and was unable to feed himself.

The pupils were now unequal, the right being larger than the left; the right pupil was inactive to light and the left sluggish. In accommodation-convergence the reflex appeared to be present but it was difficult to persuade him to perform the act of accommodation. The optic discs were normal. The arms were spastic, especially at the shoulders, with increased deep reflexes. The legs were very spastic in extension with little movement; the knee and ankle jerks were exaggerated; bilateral ankle clonus was present but the plantar reflexes were still mainly flexor. The abdominal reflexes were absent. Examination of the other systems revealed no further abnormality. The blood-pressure at this time was 145/90.

His condition gradually became worse and he died early in March, 1936.

Case 2 (*M. B., No.* 32 *in the family tree*).—Mrs. Mabel B., born in 1889 and the younger sister of Charles G. (Case 1), first came under observation on February 10, 1933, at the age of 44. She herself made no complaint beyond that for the past two years she had felt continually cold even in warm weather. It is a curious fact that, according to relatives, all the other affected members of the family are said to have had the same symptoms before the appearance of "the paralysis." M. B.'s husband, however, stated that she had recently become irritable and quick-tempered, "quite unlike herself" as he put it. Also, her memory was impaired; she repeated to her husband or children the same observations at comparatively short intervals. She

was neither restless nor emotional but rather apathetic, and had no insight regarding her irritability and her obviously faulty memory.

Physical examination showed no abnormality beyond definite and general exaggeration of the deep reflexes.

Her condition slowly deteriorated. By June, 1935, she had begun to complain of difficulty with speech. She described the latter as a difficulty with words—that she knew the words she wanted to say but could not "get them out distinctly." She also complained that her memory was unreliable and that she was unsteady in walking. It is clear, therefore, that she had temporarily developed some insight into her condition. In addition to a slurred and indistinct speech, she showed only an exaggeration of all deep reflexes, some ataxia of gait and a positive Romberg's sign.

In the latter part of 1936 she had a period of vomiting lasting about six weeks. She would vomit after each meal without abdominal pain or discomfort. Radiographic examination of the gastro-intestinal tract proved negative. Her gait had become more ataxic and she could walk only by holding on to somebody or something from time to time. The circulatory system was normal with blood-pressure 130/90. The blood W.R. was negative and the result of cerebrospinal fluid examination was as follows: Cells normal; total protein 50 mg. per cent.; W.R. and Lange reaction negative. As regards her mental condition, she was good tempered on the whole but inclined to be irritable at times, and she showed an obvious memory defect especially for recent events; she could not give the month or year or even her home address. She obeyed commands and answered simple questions (which did not depend upon memory) quite well. Her personal complaints were only those of faulty memory, difficulty with speech and "weakness of the legs."

Her present condition (March, 1940) is as follows:—

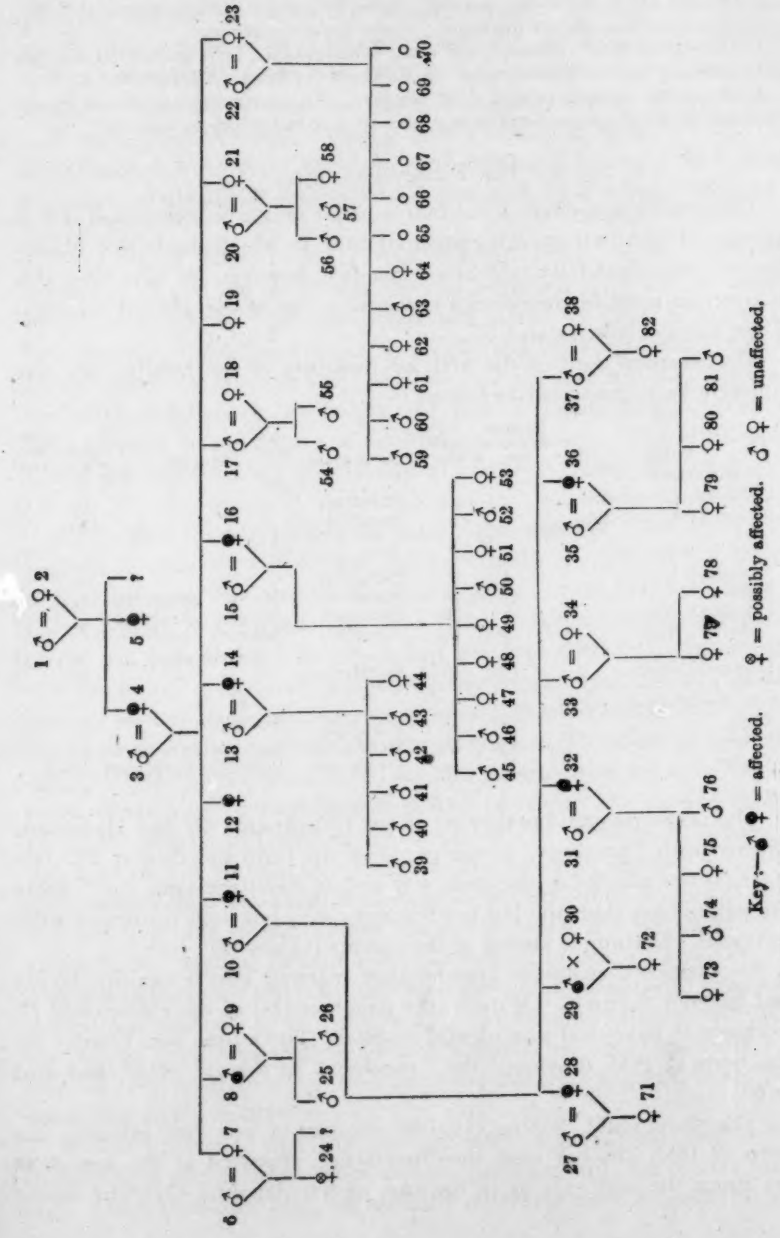
Mental state.—Her prevailing emotional tone is cheerful and she is easily amused; attention is fair but readily wanders. She can read aloud slowly with great hesitation but attempts at writing result only in an illegible scrawl. Although she holds a pen correctly she cannot write her name. Intelligence is defective. She can name correctly a pen, handkerchief and a penny but calls a box of cigarettes a cigar, and a watch a hair-clip. There are no delusions or hallucinations. Her orientation is poor; she does not know the present month or year but can give the year of her birth. She realizes that she is in a hospital but does not know its name or its situation.

Her conative activities are greatly reduced and mostly reflex and automatic. She has no interests beyond her close relatives, whom she recognizes and appears glad to see, and looking at picture papers.

Physical examination.—Pupils moderate in size, central, circular and react normally to light and accommodation-convergence. Optic fundimyopic but otherwise normal including the retinal arteries. Slight horizontal nystagmus in both directions on lateral deviation of the eyes; ocular muscles otherwise normal. Speech slow, indistinct and grossly slurred. Other cranial nerves normal. No obvious abnormality detected in sensation but adequate examination difficult owing to mental state.

The arms are slightly spastic but show full range of movement at all joints and fair power. Radial, supinator, biceps and triceps jerks exaggerated but equal on the two sides. Co-ordination of arm movements fairly good.

Gait on a widened base with shortened hesitant steps and then only with support. Romberg's sign positive. Legs spastic; full range of movement possible at all joints but power weak. Knee and ankle jerks much exaggerated but about equal on the two sides; ankle clonus well sustained on the right and present, but poorly sustained, on the left. Abdominal reflexes present and equal but sluggish.


Key:—● = affected. ◐ = possibly affected. ○ = unaffected.

Heart not enlarged; sounds normal. Pulse 85 regular; blood-pressure 150/90; palpable arteries not unduly thickened. Other systems normal.

Cerebrospinal fluid: Pressure 110 mm.; cells normal; total protein 50 mg. per cent.; globulin faint detectable trace; W.R. negative; Lange 2222100000.

Radiographic examination of skull negative. An encephalogram shows general dilatation of the ventricles similar in degree to that at autopsy in Case 1.

The Family History.

The genealogical chart of the family as far as can be ascertained is here reproduced from our previous paper of 1933, in which the family history has been described fully [4]. Since this date, however, we have been able to ascertain some further details concerning two of the affected members of the family (Nos. 11 and 28).

The essential data of the afflicted members of the family may conveniently be summarized as follows:—

Person	Number in family tree	Age at onset	First symptom	Progress	Age at death	Duration Years
First Generation						
Maternal Grandmother	4	40	Paralysis		53	13
Maternal Grand-aunt	5	*c*40	Paralysis		*c*53	*c*13
Second Generation						
Maternal Uncle	8	57	Paralysis		60	3
Mother	11	44	Paralysis	Became demented	54	10
Maternal Aunt	12	48	Dementia	Became paralysed	53	5
Maternal Aunt	14	48	Paralysis	Showed mental deterioration	66	18
Maternal Aunt	16	48	Paralysis		50	2
Third Generation						
Sister	28	44	Paralysis		54	10
Patient	29	46	Dementia	Became paralysed	54	8
Sister	32	44	Dementia	Partially paralysed	Still alive	

The maternal grandmother (4) of our two patients (29 and 32) became afflicted with "paralysis" at the age of 40 (in 1870) and died at 53. Her sister (5) was affected in the same way and at about the same age. There are said to have been another brother and sisters but their histories cannot be traced. Nothing is known of the parents (1) and (2).

Our patients' maternal grandmother married into a healthy family and had ten children. Of these, the daughter (24) of the eldest child (7) is known to have died in a mental hospital. The second son, Charles (8), was born in 1853, developed the "paralysis" at the age of 57, and died at 60.

The third child, Sophie (11), the mother of our two patients, was born in 1855. In her case, the "paralysis" appeared at the age of 44 (at about the same age as in the case of her daughter (32), our second

patient). At the age of 46 she became irritable, apathetic and disinterested. She would sit in a chair all day and would neither wash nor attend to her bodily needs. In 1905, at the age of 50, she was seen at Sir Farquhar Buzzard's out-patient clinic, National Hospital, Queen Square, and was reported as dull, lethargic and amnesic for recent events. Her articulation was defective, her arms weak and her gait ataxic. Her mental condition gradually deteriorated and she died in a mental hospital at the age of 54.

The fourth child, Julie (12), was born in 1857. Mental symptoms developed at the age of 48 and she was admitted to a mental hospital where she developed "paralysis" and died at 53. In the fifth, Alice (14), born in 1861, "paralysis" began at 48 and she lived until the age of 66. It was noted that whereas the "paralysis" in her case was the same as in the other members of the family, the mental disturbance was less pronounced and at no time was certification necessary. The sixth child, Lorris (16) was born in 1865, developed "paralysis" at 48 and died at the age of 50.

The eldest of the children of Sophie (11) and the sister of our two patients (29 and 32) was Esther (28), born in 1879. Symptoms began in 1923 at the age of 44. She was twice an in-patient in the National Hospital, Queen Square, in 1924 and 1926. The history obtained was that weakness of the legs appeared six months before her first admission. In hospital, she was found to be emotional with pronounced dysarthria and impairment of memory, especially for recent events. She was ataxic with reduced motor power in the legs but with normal reflexes. The blood-pressure was 140/75. The cerebrospinal fluid was also normal with negative Wassermann reaction and a total protein of 0·03 per cent. We are indebted to Dr. J. W. Wayte, of Croydon, for an account of the clinical features of the latter part of her illness. He states that when he first saw her, about three years before her death at the age of 54, her limbs were held stiffly and her gait was spastic. After about two years her gait changed in character and became more ataxic; she seemed to lose her sense of position and developed a slow but increasing dementia. Her speech was slow, slurred and inclined to be "scanning." She became progressively more spastic and emaciated and would emit spontaneous and apparently purposeless cries from time to time. For the last year of her life she was bedridden and incontinent.

It is of interest to note that our patients' maternal grandmother first showed signs of the disease when she was pregnant with her seventh child (17). The eighth child (19) was mentally defective, but the ninth (21) and

tenth (22) were considered to be the healthiest of her children in their youth and early adult life. Neither they nor their families have been affected. Our patients' mother developed the disease when she was pregnant with her youngest child (37).

Thus, it appears that there have been ten examples of the disease spread over three generations (4, 5, 8, 11, 12, 14, 16, 28, 29 and 32) and one possible case (24). As far as the second generation is concerned, only the elder members have been affected. The seventh, ninth and tenth members of this generation have all escaped, although their mother became affected during her seventh pregnancy. The eighth child was an imbecile and died at the age of 14 of an intercurrent malady. The children of the unaffected members of the second generation are not yet of the appropriate age. The child of the unaffected eldest sibling in the second generation died in a mental hospital.

In the majority of those affected, the "paralysis" appears to have preceded the mental disturbance and dysarthria has been an early symptom. It is more probable, as in our two patients, that the development of mental and physical symptoms has been practically coincident, but that the affection of the legs has more readily attracted attention.

With the exception of one case (8) the onset of the disease has occurred in the fifth decade. Of the nine cases who have died with the disease, the shortest course was two years, the longest thirteen years and the average eight years.

It is an interesting fact that members of the family are fully aware of the main features of their "family paralysis" and have learnt to recognize the early symptoms. They have themselves made the observation that female members of the family are more liable to be affected (eight of ten cases) and that the disease is apparently transmitted through the female. It would appear that the inheritance accords with a Mendelian recessive. No phenomena of anticipation have been observed.

Pathological Examination of Case 1.

Account of autopsy (performed by Dr. S. W. Hardwick, March 10, 1936).—The body was that of a wasted man in an attitude of extension at the hips, knees, ankles and arms with the fingers flexed; rigor mortis was present. The muscles were found on exposure to be very dry, especially the temporals. There was a striking absence of subcutaneous fat.

The skull was extremely dense and almost ivory throughout, taking much longer to saw through than usual; the same hardness of bone was noted in removing the spinal cord. The dura mater was normal but the pia-arachnoid was somewhat milky in appearance over the frontal lobes. The brain (weight 1,340 grm.) and spinal cord were preserved intact in formal saline for further study. No gross arterio-

sclerosis was evident in the larger arteries of the brain and the pituitary body was normal in appearance.

The thyroid gland was normal in size and appeared healthy. The bronchi, hilar lymph nodes and root vessels were also normal. The pleuræ were healthy ; the right lung was collapsed against the posterior wall of the chest and was airless; the left lung contained a small central patch of bronchopneumonia in the lower lobe, the upper lobe being œdematous, reddened and congested, and exuding frothy material. The pericardium was normal. The heart (weight 285 grm.) was small with a general atrophic appearance ; the musculature was pale but firm. The valves and endocardium were natural and the orifices of the coronary arteries were patent without atheroma. The aorta was also free from atheroma throughout the whole of its length.

The abdomen contained no free fluid and the peritoneum was normal. The liver (weight 1,210 grm.) was firm with a definite nutmeg appearance. The spleen (weight 140 grm.) was normal. Both right (115 grm.) and left kidneys (110 grm.) seemed healthy, also the suprarenals and pancreas. The stomach was normal in appearance. The small intestines were generally thin-walled, the lumen of the ileum being small, and occasionally small submucosal hæmorrhages were seen throughout the jejunum. The large intestine was full of scybala ; many small hæmorrhages were observed in the submucosa but no definite ulceration. Peyer's patches were not unduly prominent. The mesenteric lymph nodes were normal and the bladder and prostate healthy.

Macroscopic appearance of brain after fixation.—The brain was asymmetrical the left cerebral hemisphere being larger than the right. The left measured 190 mm. antero-posteriorly and 69 mm. transversely, whereas the corresponding measurements for the right hemisphere were 184 mm. and 60 mm. respectively. Pacchionian bodies were present in numbers normal for the age of the patient. The frontal lobes were flattened, with slight atrophy of the convolutions, and a "milky thickening" of the leptomeninges. The vessels of the brain, including the circulus arteriosus, were normal in distribution and all appeared healthy to the naked eye.

The brain stem was severed and the pons and medulla cut serially across ; they presented no naked eye abnormalities. On incising the cerebellar hemispheres at right angles to the surface, it was noticed that the arborizations were finer than normally on account of a definite shrinkage of the white matter. There were two minute cyst-like spaces situated in the subcortical white matter of the left cerebellar hemisphere.

The cerebral hemispheres were then separated by a mid-line incision in the sagittal plane which revealed a great and uniform atrophy of the corpus callosum. The right cerebral hemisphere was cut in the horizontal plane in slices, each of 1 cm. in thickness, and the left hemisphere vertically in the coronal plane. On section the white matter of the hemispheres was mottled and greyish. It was mostly firm but in places had a finely reticulated appearance with minute cavities. This change was irregularly distributed and was not greater towards the centres of hemispheres ; the subcortical arcuate fibres were everywhere fairly well preserved. The frontal and occipital lobes (fig. 1) were similarly affected but nowhere was the change so intense as in diffuse sclerosis. The lateral ventricles showed some degree of dilatation.

Histology of brain.—The cerebral white matter appeared for the most part rarefied and pale when stained for myelin fibres but these had nowhere completely disappeared. In more affected parts, overgrowth of neuroglial fibres was fairly dense, especially round the blood-vessels. Occasionally, many spider cells rich in processes were present but such areas were not numerous and swollen-bodied neuroglial cells were not seen. Also, there was some increase of neuroglial fibres throughout the

white matter of the brain, even in areas which macroscopically appeared normal. Demyelination was especially severe in the corpus callosum where many microglial fat phagocytes were present.

The only other striking abnormality in the cortical and subcortical regions, apart from the cornu Ammonis, was found in the walls of the small blood-vessels where two main types of change occurred. The first consisted of a hyaline swelling of the middle coat, the cells of which had lost their nuclei, stained diffusely yellow-brown by van Gieson's method and appeared abnormally refractile. This hyaline change was seen chiefly in the small pial vessels but was also visible in many of those of the white matter, especially in relation to the partially demyelinated areas ; it also was present to a slighter degree in some of the cortical vessels, while those of the choroid plexus were severely affected.

The second change was seen only in relation to a small proportion of the vessels of the white matter and cortex. It consisted of a zone, sometimes concentric with the vessel wall but not necessarily so, in which the myelinated fibres were pushed back by amorphous-looking tissue containing many fine neuroglial fibres but no other recognizable cellular elements except a few microglial nuclei of unusual shape (figs. 2-8). In a few instances this perivascular change did not entirely surround the vessel but appeared as nodosites (fig. 9). Occasionally this change was combined with hyaline degeneration of the vessel wall, but more commonly it was seen around vessels which possessed no recognizable middle coat. On the other hand, medium-sized intracerebral vessels showing medial changes were often surrounded by a clear space which was outlined externally by an irregular layer of collagen fibres. Around all the vessels of this type there was a tendency for the collagen fibres to run out irregularly into the nervous tissue for a short distance in a more or less radial direction. Narrow clear zones were also found here and there in the outer layers of the cortex, in which they were most evident in sections stained by Mallory's phosphotungstic acid hæmatoxylin. The cerebral cortex, apart from the cornu Ammonis, showed very little change ; there was a small amount of cell atrophy and an occasional plaque of the Redlich-Fischer type but no neurofibrillary alterations. An occasional wedge-shaped scar was seen extending from the surface deeply into the cortex (fig. 6).

In the cornu Ammonis and the cerebellar cortex the appearance altered in a quantitative rather than a qualitative manner. The small pial vessels overlying the hippocampus showed considerable medial change and the majority of the small intracerebral vessels had greatly thickened walls. Very many of these vessels were surrounded by clear zones, especially inside the hook formed by the fascia dentata. In addition, clear circular or oval bodies varying in size from 12 to 100 μ were seen both internal and just external to the fascia dentata and also in the zone of the pyramidal cells. In silver preparations, many of these could not be distinguished from senile plaques but others were more structureless. With Da Fano's modification of Bielschowsky's method and with Braunmühl's stain, they were rather strongly argentophil, containing collections of irregular darkly-staining granules which were placed either centrally or peripherally or less often scattered irregularly through the "plaque." The size of the central deeply-staining mass appeared to bear no relationship to that of the structure as a whole, for there occurred some large formations with no centres and others which were small and were practically composed of the deeply-staining central mass. Most of the structures were well-defined but others merged into the surrounding tissues ; they rarely showed the typical cartwheel appearance of a senile plaque. As regards staining reactions, these plaque-like structures were faintly eosinophil and with Mallory's connective tissue stain appeared intensely blue; with Weigert's elastin stain they were black, especially

in their central parts ; with Mallory's phosphotungstic acid hæmatoxylin they stained pale pink with orange centres and were surrounded by a condensation of neuroglial fibres, while an occasional fibre penetrated into them. In the centre of many, a small capillary vessel could be seen and by Perdrau's method and its modifications, fine spicules or strands of connective tissue could often be discerned passing out into the "plaque" from the central vessel. The plaque-like structures, however, did not form cuffs round vessels as they were always circular or oval in shape even when the vessel was seen in longitudinal section. With Scharlach R these formations stained rather faintly and often in an asteroid manner, while many of the microglial cells in the neighbourhood had reddish granules in their processes.

Professor del Rio Hortega has demonstrated for us by his technique for astrocytes that these plaque-like formations consist of a densely interwoven mass of very fine fibres, presumably of neuroglial origin. Around these "plaques" there are abundant fibrillary astrocytes, the processes of many of which can be traced entering into the "plaque." The glia surrounding some of the vessels appears to condense in the form of a fine surrounding network (fig. 10). The activity of the microglia in these structures is only moderate in degree but here and there an accentuation of their reaction occurs (fig. 9c).

The plaque-like structures interrupted the line of nerve cells of the fascia dentata and smaller forms were numerous among the pyramidal cells of the cornu Ammonis. Many of the latter showed Alzheimer's neurofibrillary cell changes in varying degree (fig. 16). Throughout the cornu Ammonis there was a considerable overgrowth of neuroglial fibres and in parts there was focal atrophy of the pyramidal cell layer (fig. 10).

In the cerebellum the appearances were essentially similar to those in the hippocampus. Here the molecular layer of the cortex in many places was full of plaque-like structures, most of which appeared to be related to capillary or precapillary vessels. These bodies were also seen in smaller numbers in the granular layer. Throughout the cerebellum the neuroglial fibres in the molecular layer were more numerous and coarser than normal. They were not interrupted in their course by the "plaques" but passed through them without change in their appearance. Mallory's method with phosphotungstic acid hæmatoxylin, however, did not reveal any increase of fibres in these structures. A diminution in the depth of the molecular layer was observed which, in parts, amounted to an atrophy involving also the granular layer.

The Purkinje cells were considerably diminished in number but those present showed no pronounced change. There was, however, a considerable loss of basket fibres, most of the Purkinje cells being quite naked. A few large "torpedoes" (Cajal's "bolus de retraccion") were seen on the axons of the Purkinje cells. The Bergmann cells were increased in number in areas where the vascular changes were most pronounced. The granular cells, except where they were separated by "plaques," were normal in appearance. In the outer part of the molecular layer occasional corpora amylacea were seen. The dentate nucleus was unaffected. A few "plaques," however, were to be found in the substantia ferruginea. The basal ganglia, mid-brain, pons and medulla were otherwise healthy.

The meningeal arterioles, and especially over the cerebellum and cornu Ammonis, showed a hyaline thickening of the media which was sometimes intense and accompanied by secondary obliterative endarteritis and even recanalization. Deep to these diseased vessels were many minute areas of softening with an occasional scar composed of fibrous astroglia.

In the spinal cord, sections stained by Bielschowsky's method showed a few

"plaques" in the anterior horns and slight changes in the motor cells. The overlying pial vessels again showed hyaline changes in their middle coats.

The ependyma was everywhere healthy. In the choroid plexus the blood-vessels, as already noted, showed pronounced hyaline changes and numerous corpora amylacea were also present. The epithelium, however, was healthy.

Commentary.

The family history of the cases described would be remarkable in any form of presenile dementia apart from Huntingdon's chorea. In the absence of final histological proof we realize that it is impossible definitely to assert that the other nine affected members of the family suffered from precisely the same disease as the case which came to autopsy, but at least the sister (Case 2 and No. 32 in the family tree), whom we have observed for seven years, exhibits a clinical condition identical with that of her brother (Case 1). Also, the clinical descriptions of the remaining eight members of the family who were apparently affected indicates that all suffered from the same type of malady. It is reasonable, therefore, to conclude that the same pathological process is common to all ten cases.

Although most heredofamilial diseases of the central nervous system are associated with pathological changes of the type to which the term "abiotrophy" has been applied, a different mechanism would appear to be present in the disorder we have described. The case (Case 1) we have considered fully presents a combination of clinical features and pathological changes quite unlike any condition hitherto recorded in the literature.

The clinical features of the disorder can be explained by the extensive demyelination of the cerebral white matter and especially of the corpus callosum. These changes sufficiently account for the progressive dementia and the motor disturbances, while the ataxia is related in some degree to the pathological changes in the cerebellum. From the clinical condition of Case 1, it could not be doubted that the lesions were widespread; during life it was considered probable that the underlying cause of the disorder was a universal demyelination having some resemblance to Schilder's periaxial encephalitis but the alternative possibility of a disseminated degeneration of neurones was borne in mind. The pronounced family history favoured the former view which proved to be correct in so far as a superficial examination of the brain revealed widespread dissolution of the white matter but with a state of preservation of the nerve cells remarkable after a malady of such duration. The cause of the demyelination, however, appears to be a most unusual change affecting the small arterioles of the pia mater and the white matter, and to a lesser extent of the cerebral

cortex. As in the disorder reported briefly by Binswanger (1895), termed "encephalitis subcorticalis," and later substantiated by Alzheimer (1902), Nissl (1920), and Farnell and Globus (1932), the incidence of the pathological lesions falls heavily upon the subcortical arterioles, suggesting even a selective involvement of these vessels. Of the two main types of change, the hyaline sclerosis was not universal but it affected a large proportion of the blood-vessels in the areas of myelin degeneration. In other parts more pronounced changes were present around vessels and amounted to zones of amorphous-looking material in which fine fibrils, presumed to be glial in origin, could be identified in densely woven masses. These perivascular structures had some resemblance to the Redlich-Fischer senile plaques and indeed some, especially those found in the pyramidal cell layer of the cornu Ammonis, may well have been identical with them, the more so as in this part the neurofibrillary change of Alzheimer was conspicuous. The majority of these perivascular formations, however, differed so much from ordinary senile plaques, especially in their predilection for the white matter, that they must be regarded as different structures. That some of the classical senile plaques should be present is not unexpected in a person of this age (54) who has been demented for some years, and if the Grünthal theory of their origin on the basis of Ruzicha's conception of protoplasmahysteresis be correct, the gross disturbance of metabolism of the brain which must be associated with histological changes of the extent occurring in this case is a pre-requisite for their formation. The same disturbance of brain metabolism would account for the neurofibrillary alterations which were noted in the cornu Ammonis. It is noteworthy that this patient exhibited the neurofibrillary changes with which we are familiar in Alzheimer's disease and in senile dementia, but their prevalence was considerably less and, indeed, beyond the fact that both Alzheimer's disease and the case we are discussing indicate a severe disorder of the brain metabolism, no resemblance either clinically or histologically can be drawn between them.

Binswanger's original account of "encephalitis subcorticalis" is based on a description of two cases, one a variant of "general paralysis" which he believed should be distinguished from the parent disease, and the other an example of arteriosclerotic degeneration of the brain. In those days (1895) it was believed that syphilis accounted for many, but not necessarily all, cases of "general paralysis," but whether or not Binswanger was describing a syphilitic disease of the subcortical arterioles is uncertain. It would appear that syphilis is capable of producing the picture of "encephalitis subcorticalis," an example being reported in 1936 (Board of

Control Reports), but Nissl's case and that of Farnell and Globus concerned patients whose serological tests for syphilis were negative. The latter authors emphasize the fact that Binswanger's "encephalitis subcorticalis" (which may also be termed "chronic progressive vascular subcortical encephalopathy") has no clinical features which serve to distinguish it from other forms of cerebral arteriosclerosis. Nissl, however, commented on a characteristic lack of insight and a euphoria of several years duration. From the histological aspect, Binswanger's "encephalitis subcorticalis" shows arteriosclerotic changes in the affected vessels, the demyelination being secondary to this. No record can be traced of this disease being associated with perivascular formations of the type seen in our case or of its having a familial incidence.

We conclude, therefore, that the familial disorder we describe is not Binswanger's encephalitis nor does it show any resemblance to polyarteritis nodosa. The pronounced familial incidence of the malady places it among hereditary and familial diseases. Considering the extensive involvement of the white matter of the brain, it may be compared with Schilder's encephalitis, using this term in its broader sense to include all forms of diffuse sclerosis of the white matter. Here, however, we can trace little resemblance between the disease seen in our patient and that in other cases of diffuse sclerosis except perhaps in the atypical example reported by Lowenberg and Fulstow. In their patient the illness began at the age of 26 years with right hemiparesis, hemianæsthesia, incoherent speech and delusions. Later, epileptiform seizures developed together with wasting of the small muscles of the right hand and of the right shoulder girdle. Dementia with incontinence followed with death at the age of 37 years. On post-mortem examination, the central portions of the white matter of the cerebral and cerebellar hemispheres, especially on the left side, were yellow-grey in colour and of increased consistency. The vessels appeared as glassy, transparent lines or discs according to the plane of section. In the left cerebellar hemisphere, the myelin was almost entirely replaced by peculiar bodies which the authors attributed to an abnormal metabolism of myelin; associated with this was a dense neuroglial sclerosis. There was no evidence in this case that the change began in the blood-vessels. The authors quote Kaltenbach, Alzheimer, Baranconi and Witte as having described similar metabolic products of myelin. These bodies, however, do not appear to resemble the "plaques" found in our own case, in which the degeneration of myelin was clearly not a primary process but rather one secondary to the vascular changes. The presence of perivascular formations in the cerebral and cerebellar cortex in our case

is additional evidence against the view that the vascular changes might be secondary to degeneration of myelin.

The behaviour of the neuroglia merits attention. Throughout most parts of the brain the astroglial hyperplasia was of mild degree. Around many vessels, however, there was a considerable condensation of fibres which appeared to be of neuroglial origin. Around some of the vessels the appearance was that of a tangled mass of fine fibres, the few nuclei which were present in this zone being of microglial rather than astrocytic type. The microglia in most of the "plaques," however, showed only a moderate degree of activity. On the other hand, specific stains showed fine connective tissue fibres passing out from the vessel walls into the surrounding "plaque." The latter therefore consist of fine fibres, presumably of neuroglial origin, a few thicker processes from neighbouring astrocytes, radiating connective tissue fibres and microglial cells. As to whether there is, in addition, a background on which these various elements are set cannot be determined with the histological methods available.

There is little evidence to indicate the manner of development of these plaque-like structures. They might result from an abnormal lability of the perivascular neuroglia or represent the reaction of these and other tissues to toxic substances passing through the diseased walls of the vessels. It appears certain that the changes in the vessels and the plaque-like structures are very closely related, but the preponderance of one or the other change in different parts of the brain makes it impossible to assign the dominant role to either process.

Kinnier Wilson, in his textbook published posthumously, has regarded the familial disorder which we have described as a possible variant of the so called "spastic pseudosclerosis" of Creutzfeld and Jakob. At the time of writing he had access only to the clinical description published in 1933 as the pathological material was not then available. A familial incidence of the spastic pseudosclerosis of Creutzfeld and Jakob has not been recorded except in a doubtful instance by Meggendorfer (1930) in which the disease affected a brother and sister; in the preceding generation their mother and seven of her nine siblings all died from "paralysis." The Creutzfeld-Jakob syndrome is, however, pre-eminently a cortico-striato-spinal degeneration without noteworthy changes in the blood-vessels. The pathological process is diffuse and non-selective and the corpus striatum, together with the thalamus and hypothalamus are involved. The histological findings in our case effectually dispose of any suggestion as to its relationship with the syndrome described by Creutzfeld and Jakob.

We desire to express our indebtedness to Dr. P. M. Turnbull, Medical

Superintendent of Tooting Mental Hospital, for the facilities he afforded one of us (C. W-D.) in keeping Case 1 under observation; to Dr. S. W. Hardwick for his account of the autopsy; and to Professor del Rio Hortega for the interest he has shown in the investigation and for the assistance granted to one of us (W. H. McM.).

Summary.

(1) The clinical features, together with the post-mortem and histological findings, of an unusual case of presenile dementia with spastic paralysis are described.

(2) The pathological changes found include widespread demyelination of the brain and the presence of peculiar perivascular structures which occurred chiefly around the smaller blood-vessels of the subcortical white matter, the molecular layer of the cerebellum and the cornu Ammonis.

(3) The condition of a sibling exhibiting clinical features identical with those found in the previous case is also described.

(4) The family history of these cases is reviewed and eight clinically similar cases are mentioned.

(5) The relationship of the disease we describe to allied disorders is discussed.

(6) The opinion is expressed that the ætiology of the disease probably lies in a disturbance of the smaller blood-vessels of the nervous system which, in turn, is attributable to the absence of some specific factor or is the result of an abiotrophic manifestation.

Addendum.—Since the above communication was completed a further example of the disease in the same family has come under our observation. The patient is the younger sister of Cases I and II and appears as No. 36 in the family tree. Thus, four examples of the disease have now occurred in the third generation, three of which have been personally observed. The total number of probable cases is now eleven over three generations.

The present condition of this additional case is as follows: Mrs. V. B. aged 45, complains that she always feels cold and that her legs are "shaky" especially on attempting to walk. Also, that her memory is poor and that she has difficulty in expressing herself. A niece informs us that Mrs. V. B.'s mental condition has been slowly deteriorating for the past two years, that whereas formerly she was always bright and talkative, she is now very quiet and scarcely speaks at all. She shows little interest, is usually depressed and may cry at times. Her memory is

defective; she forgets nearly everything she is told and repeats statements two or three times within a short interval, evidently having forgotten she has made the same observation a short time before. Although she goes to the cinema occasionally, she exhibits little appreciation of the performance.

Physical examination shows a tremor of the tongue on protrusion; speech is slurred and indistinct but the other cranial nerves are normal. All movements are present but the deep reflexes are definitely exaggerated. There is some increase in muscular tone and poor co-ordination of the legs with unsteadiness in the Romberg position. The superficial reflexes are normal and sensory stimuli are appreciated. The heart and palpable arteries are normal; pulse 76; blood-pressure 145/80.

Her early dementia, dysarthria, increased deep reflexes and slight inco-ordination of the legs represent the same stage of the disease at which Cases I and II were first observed.

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LEGENDS FOR PLATES.

FIG. 1.—Occipital cortex, showing demyelination. (Loyez's method for myelin.)

FIG. 2.—Precentral gyrus. Typical examples of the perivascular structures mentioned in the text. They are situated in the superficial part of the white matter immediately deep to the cortex. The structure on the left has an appearance of finely radiating fibres; the one on the right is more homogeneous and contains a few microglial nuclei. (Loyez's method for myelin.)

FIG. 3.—Inferior temporal gyrus. The deep aspect of the cerebral cortex with a cluster of the formations surrounding blood-vessels. (Hortega's method for astrocytes.)

FIG. 4.—Inferior temporal gyrus. Small glial scar dimpling the surface of the brain. (Hortega's method for astrocytes.)

FIGS. 5, 6, 7 and 8.—Details of the perivascular structures. Fig. 5 shows a dense halo of tangled fibres, presumably of glial origin, surrounding a thickened blood-vessel. Fig. 6 illustrates a small vessel situated excentrically in a dense mass of fibres and surrounded by astrocytes which have undergone fibrous transformation. In Fig. 7 the perivascular structures are represented by a tangled mass of fibres, while Fig. 8 shows a group of three tending to fuse together. (Hortega's method for astrocytes.)

FIG. 9.—Frontal cortex. White matter in which functionally active microglia is aggregated in small perivascular nodes; in the lower of the two nodes in (*c*) the microglial activity is exceptional for this case. (Hortega's method for microglia.)

FIG. 10.—The cornu Ammonis, showing focal atrophy of the cortex and the presence of large plaque-like structures in relation to the fascia dentata. (Mallory's phosphotungstic acid hæmatoxylin.)

FIG. 11.—The cornu Ammonis, showing details of the plaque-like structures near the fascia dentata. (Mallory's phosphotungstic acid hæmatoxylin.)

FIG. 12.—The cornu Ammonis. An apparently structureless mass in the white matter with activity of microglia and surrounding neuroglia. (Bielschowsky-da Fano method.)

FIG. 13.—The cornu Ammonis. Plaque-like structures in the pyramidal cell layer with astroglial and microglial reaction. There are many astrophied nerve cells and some neurofibrillary alterations. (Bielschowsky-da Fano method.)

FIG. 14.—The cornu Ammonis. Alzheimer loops and tangles in the pyramidal cell layer together with a few plaque-like structures. Some of the latter could be accepted as Redlich-Fischer senile plaques. (Bielschowsky-da Fano method.)

FIGS. 15, 16 and 17.—The cerebellum. Sections showing perivascular gliosis in the molecular layer. The node-like character of this lesion can be seen in several places. In Fig. 16. the hyperplasia of the Bergmann cells is noteworthy. (Hortega's method for astrocytes.)

FIG. 18.—The cerebellum. Section showing a mass of connective tissue in the centre of a "plaque" with sclerosis and surrounding gliosis of a neighbouring precapillary vessel. (Hortega's double impregnation method.)

PLATE VIII.

FIG. 1.

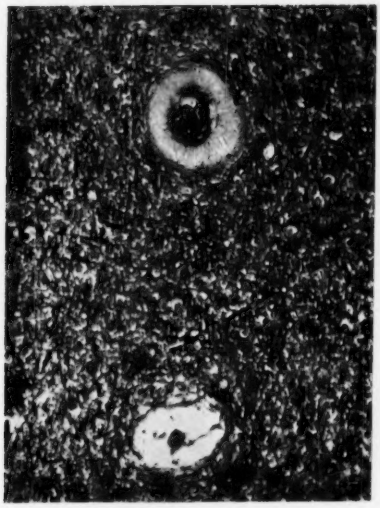


FIG. 2.

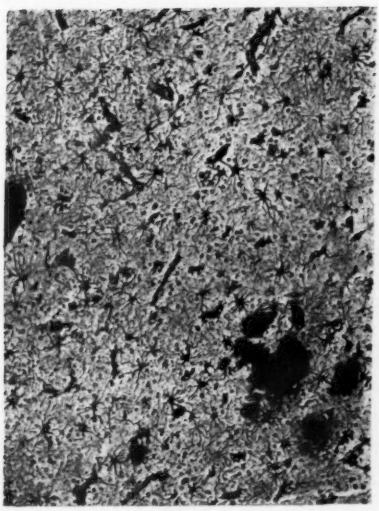


FIG. 3.

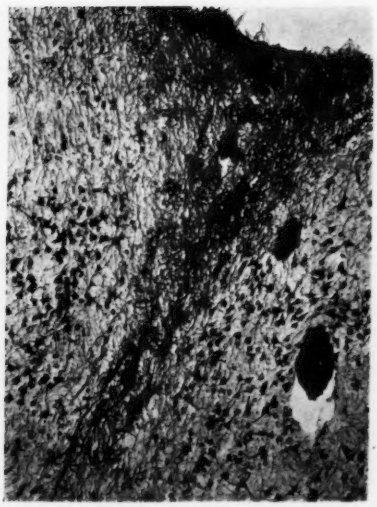


FIG. 4.

To illustrate article by C. Worster-Drought, J. G. Greenfield and W. H. McMenemey.

PLATE IX.

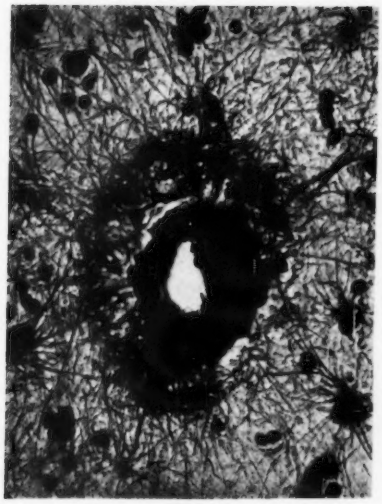


FIG. 5.

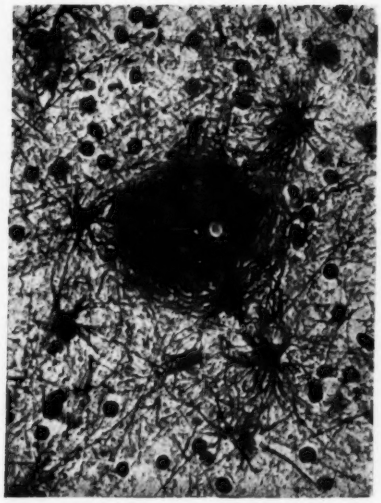


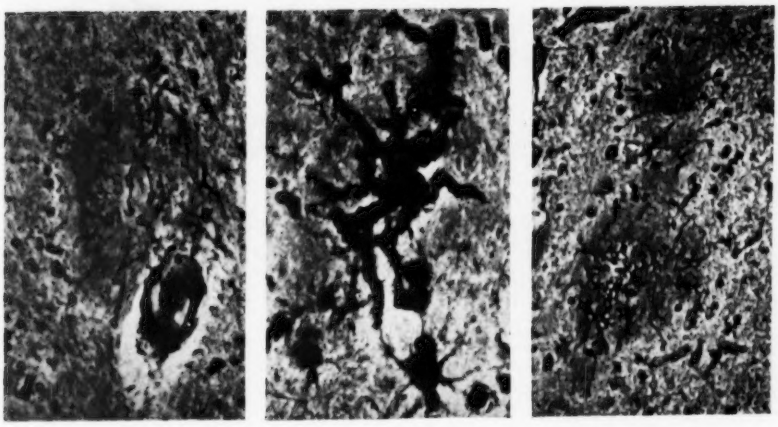
FIG. 6.

FIG. 7.

FIG. 8.

To illustrate article by C. Worster-Drought, J. G. Greenfield and W. H. McMenemey.

PLATE X.



(*a*) (*b*) (*c*)

FIG. 9.

FIG. 10.

To illustrate article by C. Worster-Drought, J. G. Greenfield and W. H. McMenemey.

PLATE XI.

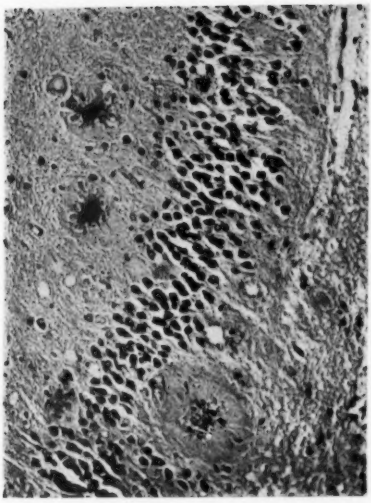


FIG. 11.

FIG. 12.

FIG. 13.

FIG. 14.

To illustrate article by C. Worster-Drought, J. G. Greenfield and W. H. McMenemey.

PLATE XII.

FIG. 15.

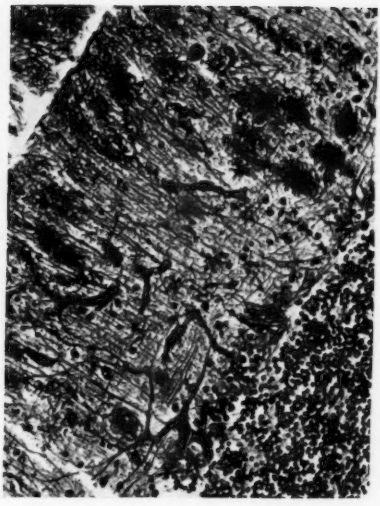


FIG. 16.

FIG. 17.

FIG. 18.

To illustrate article by C. Worster-Drought, J. G. Greenfield and W. H. McMenemey.

THE RELATION OF ATROPHY TO FIBRILLATION IN DENERVATED MUSCLE.

By D. Y. SOLANDT AND J. W. MAGLADERY.[1]

(Departments of Physiology and Physiological Hygiene, University of Toronto, Toronto, Canada.)

WHEN a skeletal muscle is deprived of its motor nerve supply it undergoes certain anatomical and functional changes which are retrograde in character and may be termed collectively the degeneration of denervation. Prominent among the degenerative changes are the atrophy and the fibrillation. Atrophy is the principal anatomical change and consists chiefly of a marked decrease in the size and eventually in the number of muscle fibres. Fibrillation was first observed by Schiff (1851) and consists of random inco-ordinated contractions, or partial contractions, of fibres throughout the denervated muscle. These contractions can be seen by reflected light on the exposed muscle. The fibrillary contractions are accompanied by action potentials (Brown, 1937 ; Denny-Brown and Pennybacker, 1938) and amplification of these potentials offers a delicate method for detecting fibrillation.

Langley and Kato (1915 *a, b*) associated the beginning of atrophy with the onset of fibrillation. Later Langley (1916) concluded that the atrophy was due to the fibrillation and was thus an atrophy of fatigue and not of disuse. This thesis was supported when Langley and Itagaki (1917), measuring arterio-venous oxygen differences, found that denervated muscle showed a higher oxygen consumption than normal muscle. Hines and Knowlton (1934, 1935), however, detected no change in the oxygen consumption of rat muscle over a period of twenty-eight days following denervation. Furthermore, they found only minimal changes in glycogenolysis and lactic acid formation. Chor, Dolkart and Davenport (1937) found negligible nitrogen and phosphorous changes. More recently Fischer (1939) has shown that restricted electrical exercise, which is effective in decreasing the muscular atrophy following denervation, produces an increase in the oxygen consumption of the affected muscle.

[1] Aided by a grant approved by the Committee on Research for the Prevention and Treatment of After-Effects of the National Foundation for Infantile Paralysis, Inc., New York.

Thus, while there is a body of evidence contrary to Langley's hypothesis that the atrophy of denervation is due to the work involved in the fibrillation, no direct proof for or against this hypothesis is available. The object of the present experiments (Solandt and Magladery, 1940) was to prevent the fibrillation in denervated muscle and to observe the rate of atrophy under these conditions.

Methods.

Albino rats weighing between 200 and 300 grm. were used throughout. They were maintained on adequate diets and kept in small separate cages. The gastrocnemius-soleus group of muscles was denervated by removing a length of the sciatic nerve (approximately 0·5 cm.) high in the thigh. As a rule, only one side was denervated, the other side being used as a control.

Muscle atrophy was estimated by comparing the fresh wet weights of muscles from the denervated (D) and normal (I) sides. The result is given in the tables as the decimal fraction of the ratio D/I. In any one series involving a number of animals half the total number had the right and half the left side denervated. By comparing muscle weight with animal weight it was estimated that, with careful dissection, the error in muscle weight determination was not greater than $\pm$ 2 per cent.

Fibrillation was routinely detected by the electrical amplification of the action potentials of fibrillation led from the muscle through two fine needle electrodes. Photographic records were made using a Matthews oscillograph. For the repeated routine examination the action currents were made audible with a loudspeaker. We found this electrical method for detecting fibrillation more useful than the mere observation of fibrillary movement. When checked by exposure of the muscle the electrical method was shown to be the more sensitive. Furthermore, as the electrical procedure required no skin incision, it could be repeated on any one animal as often as necessary.

Light ether anæsthesia was used during the denervation operation and also, unless the animal was already drowsy from other drugs, while the needle electrodes were in place.

Results and Discussion.

(*a*) *Production of atrophy.*—Fig. 1 shows graphically the course of weight loss in the gastrocnemius-soleus muscle group of the rat following denervation by sciatic nerve section. The results confirm the findings of many previous workers who have reported that the weight of a denervated muscle is reduced to about half that of the normal control fourteen days after denervation. Weight loss is detectable by our methods about five days after denervation. As indicated, each major point on the curve represents the average of a number of determinations, the outside limits of which are shown. It will be seen that the spread of results is not great and the degree of atrophy can be predicted with considerable accuracy for any given time after denervation.

(*b*) *Production and arrest of fibrillation.*—Fig. 2 shows typical records

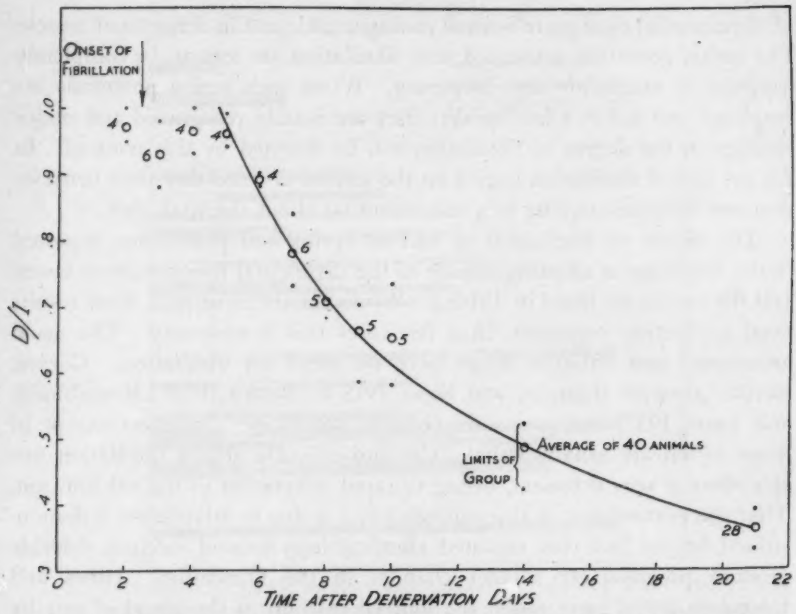


FIG. 1.—Course of the denervation atrophy in gastrocnemius-soleus muscles in rats. D/I is the ratio of the weight of the denervated muscle to that of the normal muscle of the opposite side expressed as a decimal fraction. The average of each group is shown by the circle, the limits by the dots and the number of animals involved is indicated for each average.

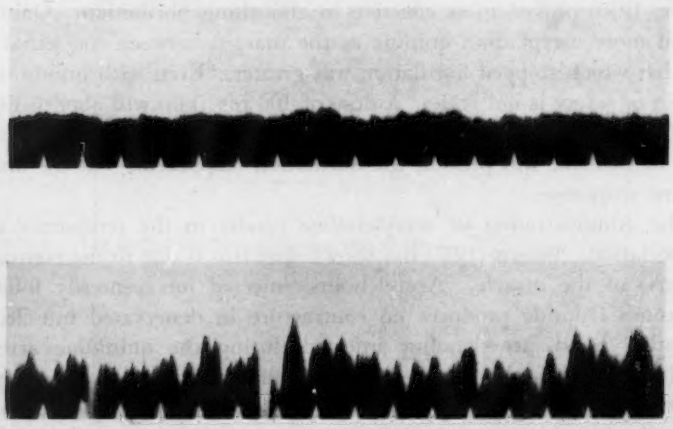


FIG. 2.—Action potentials from gastrocnemius-sóleus muscles of the rat. Upper record = control base-line on intact side; lower record = fibrillation in muscle denervated by section of the sciatic nerve four days previously. Time intervals = 0·2 seconds.

of the electrical changes in normal resting muscle and in denervated muscle. The action potentials associated with fibrillation are seen to be completely irregular in amplitude and frequency. When such action potentials are amplified and led to a loudspeaker they are readily recognized and major changes in the degree of fibrillation can be detected by this method. In the rat typical fibrillation begins on the second or third day after denervation and increases rapidly to a maximum on about the sixth day.

The effects on fibrillation of various agents and procedures, reported in the literature as affecting muscle or the myoneural junction, were tested and the results are listed in Table I. While, for the most part, these results need no further comment, in a few cases this is necessary. The usual anæsthetic and sedative drugs have no effect on fibrillation. Curare, eserine, atropine (Langley and Kato, 1915 *a*; Brown, 1937; Rosenblueth and Luco, 1937) and potassium chloride are all without effect except in doses which are usually lethal. Calcium chloride arrests fibrillation but this effect is very transient, owing to rapid adaptation to the calcium ion. That the evanescence of this calcium effect is due to adaptation is demonstrated by the fact that repeated identical injections of calcium chloride produce progressively smaller changes in the fibrillation. Hines and Knowlton (1939) have raised the ionized calcium in the blood of rats by injecting parathormone. Here the rise in calcium is probably so slow that the tissue adapts itself to the change in environment without any obvious alteration in fibrillary activity.

Of all the agents tested quinine (Harvey, 1939) and quinidine (Buchbinder, 1930) proved most effective in abolishing fibrillation. Quinidine proved more useful than quinine as the margin between the lethal dose and that which stopped fibrillation was greater. Even with quinidine the margin of safety is not wide. A dose of 100 mg./kilo will abolish fibrillation for as long as nine hours, but this makes the animals drowsy. Repeated doses of this size will prevent the fibrillation reappearing but the animals become stuporose.

The administration of acetylcholine results in the temporary arrest of fibrillation. Brown (1937) has shown that this is due to the contracture response of the muscle. Acetylcholine injected intravenously following potassium chloride produces no contracture in denervated muscle. On the other hand, acetylcholine injected during the quinidine arrest of fibrillation evokes the usual contracture-like response. Apparently the mechanisms by which acetylcholine and potassium stop fibrillation may be similar but they certainly differ from that of quinidine.

Tower (1939) found that traction on the tendon of a denervated fibrilla-

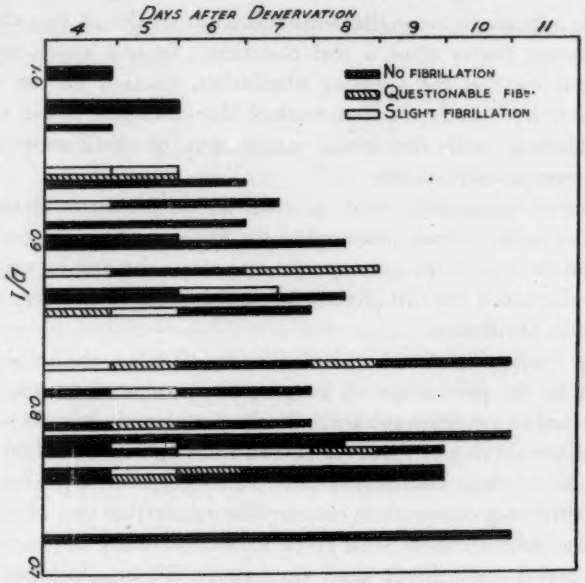


FIG. 3.—Relation of muscle atrophy and fibrillation following denervation. Each block column indicates one experimental animal. Note progressive increase in atrophy after denervation regardless of fibrillation.

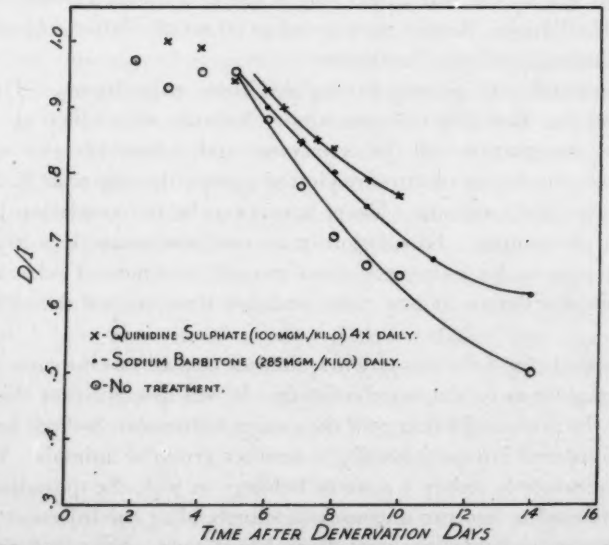


FIG. 4.—Muscle atrophy following denervation in animals treated as indicated. Each series involved more than 40 animals.

ting muscle appeared to stop the fibrillation, but suggested that this might be an apparent rather than a real cessation. In our experience, using the electrical method for assessing fibrillation, traction has no effect on fibrillary activity. Such traction renders the epimysial fascia taut, and this interference with the visual assessment of fibrillation probably explains Tower's observations.

The denervated muscles were exercised by electrical stimulation, using 25 cycle sinusoidal current interrupted for five seconds every five seconds and applied for two minutes three times a day. In our experience this procedure decreased the atrophy considerably (*see also* Fischer, 1939) but did not affect fibrillation.

(*c*) *The relation of atrophy to fibrillation.*—To test the importance of fibrillation in the production of atrophy in denervated muscle, 100 rats were subjected to a definite routine. On the first day all animals were given one, on the second day two and on the third day three doses of 50 mg./kilo of quinidine sulphate intraperitoneally in 25 per cent. aqueous solution. After the third day denervation on one side was carried out. Larger doses of quinidine sulphate were then given four times daily at 9 a.m., 2 p.m., 7.30 p.m. and 1 a.m. Each dose was usually 100 mg./kilo but this was decreased if the animal became completely comatose. Commencing on the second day after denervation all animals were tested for fibrillation at 8.30 a.m. (i.e. at the end of the longest interval between doses of quinidine) for fibrillation. Results were noted as (*a*) no fibrillation, (*b*) questionable fibrillation, (*c*) slight fibrillation.

The animals were drowsy throughout these experiments. They lost weight and the mortality rate was high. Animals were killed at varying times after denervation and the denervated and normal muscles weighed. Fig. 3 shows the degree of atrophy plotted against the degree of fibrillation on one series of 25 animals. There appears to be no correlation between these two phenomena. Fibrillation in no case was more than slight and then was present for only very short periods of time. Twelve animals showed no fibrillation at any time and yet these all exhibited marked atrophy.

As shown in fig. 4 the atrophy in quinidine treated rats does not advance quite as rapidly as in untreated animals. It was thought that this might be due to the profound lethargy of the drugged animals. Sodium barbitone was administered intraperitoneally to another group of animals. We were unable to induce as steady a state of lethargy as with the quinidine. The animals tended to become unconscious shortly after the injection and yet to be quite active before the next dose of barbitone. Nevertheless, in this

series the decrease in the atrophic process was quite comparable to that seen with quinidine sulphate.

Conclusions.

The degree of atrophy following the denervation of skeletal muscle in the rat is remarkably constant. Two weeks after cutting the sciatic nerve the gastrocnemius-soleus muscle group is reduced to one half its normal weight. This weight loss starts on about the third day after denervation and follows a regular course (fig. 1). These results confirm the findings of previous investigators.

Denervated muscle also shows a fine random twitching of the muscle fibres which starts at about the same time as the atrophy. Fibrillation may be detected by viewing the exposed muscle in reflected light or, more readily, by the electrical detection of the action potentials associated with fibrillary activity (fig. 2). Fibrillation may be temporarily stopped by the administration of various agents of which quinine and quinidine, given in aqueous solution intraperitoneally, are the most effective (Table I). Quinidine proved the more useful drug for repeated administration and through its use muscles could be kept from fibrillation for periods up to two weeks after denervation.

Langley (1916) thought that the weight loss seen in denervated muscle was an overwork atrophy caused by the continuous fibrillation. Seeking a direct answer to the relation of atrophy to fibrillation in denervated muscle, we weighed a number of denervated muscles in which fibrillation had been decreased or prevented by quinidine administration. Marked atrophy was present in all these muscles although many of them had never exhibited fibrillation as detected by our methods (fig. 3). We conclude that the atrophy of denervation is not due to the fibrillary activity.

The weight loss of the denervated muscles in the animals given quinidine, although pronounced, was not as great as in animals to which no quinidine had been given. This was attributed to the fact that the quinidine induced a lethargic condition which rested the denervated muscle or protected it from mechanical injury. This conclusion was supported by the fact that repeated administration of hypnotic doses of sodium barbitone, while not affecting fibrillation, did decrease the atrophy to an extent similar to that observed when quinidine was used (fig. 4).

Summary.

Motor denervation produces fibrillation and a loss of weight in skeletal muscle of the albino rat. The fibrillation may be prevented by the

administration of adequate amounts of quinidine. In the absence of fibrillation the atrophy is still marked. It is concluded that the loss in weight is not due to the fibrillary activity.

TABLE I.—INFLUENCE OF VARIOUS AGENTS AND PROCEDURES ON FIBRILLATION IN DENERVATED MUSCLE.

Agent	Effect on fibrillation evaluated by observing fibrillary action potentials	Notes, dosage, etc.
Ether anæsthesia	Nil	Inhalation prolonged and repeated
Sodium Barbitone	Nil	50 mg. intraperitoneally to 200 g. rat
Pentabarbitone	Nil	10 „ „ „ „ „
Sodium Bromide	Nil	300 „ „ „ „ „
Curare	Nil	Quantity adequate to block synaptic transmission
Eserine	Nil	1 mg. intraperitoneally to 200 g. rat
Atropine Sulphate	Nil	20-100 mg. „ „ „ „
Potassium Chloride	Temporarily arrests fibrillation in dose which is frequently lethal	100 mg. „ „ „ „
Calcium Chloride	Temporarily arrests fibrillation; very rapid adaptation	50 „ „ „ „ „
Barium Chloride	Nil	10 „ „ „ „ „
Magnesium Sulphate	Nil	100 „ „ „ „ „
Wheat Germ Oil	Nil	Massive dosage *per os* and subcutaneously given daily over a period of 3 weeks
Desoxycorticosterone	Nil	1·25 mg. intraperitoneally daily for 2 weeks to 200 g. rat
Quinine Hydrobromide	Abolishes fibrillation for ½ to 4 hr.	20 mg. intraperitoneally daily for 2 weeks to 200 g. rat
Quinidine Sulphate	Abolishes fibrillation for up to 9 hr.	25 mg. intraperitoneally daily for 2 weeks to 200 g. rat
Acetylcholine	Abolishes fibrillation for 10 to 30 min.	Intravenous administration up to lethal dosage
Procedure		
Adrenalectomy	Nil	Animals observed for 2 weeks following operation
Femoral Artery Ligation	Nil	Animals observed for 2 weeks following operation
Traction on Tendon	Nil	Stops visible fibrillary movement
Low Choline Diet	Nil	Administered for 3 weeks before and after denervation
Electrical Exercise	Nil	Sinusoidal current applied for 2 minutes 3 times a day for 2 weeks. Atrophy decreased

We are very grateful for the interest taken in this work by Professor C. H. Best.

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EXPERIMENTAL LESIONS IN THE BASAL GANGLIA OF THE CAT.

BY E. G. T. LIDDELL AND C. G. PHILLIPS
(From the University Laboratory of Physiology, Oxford.)

FOREMOST among experiments upon the corpus striatum are rightly placed those of Kinnier Wilson (1914). In his well-known paper on the subject, he describes his observations upon the effect of electrolytic lesions which had been placed by Horsley at his request in the lenticular nucleus of twenty-five rhesus monkeys. Such lesions, although of considerable size, failed to produce any sign of involuntary movements or rigidity analogous to those of progressive lenticular degeneration in man. "Some of the monkeys, however, showed a preference, in the taking of nuts and bananas, for the homolateral limb, or in the climbing about their cage they showed the least awkwardness or clumsiness with the contralateral limbs." In some recent unpublished work by Botterell (Fulton, 1938) similar results were obtained.

Wilson's monkeys were only allowed to survive the operation by three weeks—they were required for Marchi studies—and no bilateral lesions were made. Lewy (1923) later made bilateral lesions, but did not place his lesions by the aid of a stereotaxic instrument, as Horsley had done. He used a bistoury, and thereby wrought incidental damage. His monkeys showed conspicuous rigidity and tremor. Edwards and Bagg (1923) introduced radium needles into the striatum in nine dogs. Such a method leads to progressive destruction, maybe with compensation *pari passu*. More recently Morgan (1927) has made unilateral lesions in the cat, though without recourse to the accuracy of the stereotaxic method. His method was to pass a curved probe through a drill-hole in the temporal fossa, entering the brain through the posterior rhinal sulcus. He has recorded extensive clinical signs, including athetosis, tremor, ipsilateral muscular rigidity, circling to either side indiscriminately, dysphagia and disturbances of the voice. After eight or ten days, however, these signs had almost vanished.

Four further papers bearing on striatal injury may be mentioned. Rioch and Brenner (1938) performed unilateral decortication on five guinea-pigs. Ten days were allowed for degeneration of cortifugal fibres:

the ipsilateral striatum was then frozen by contact with a probe chilled in in CO_2 snow and ether. No new functional deficit resulted. From this the authors concluded that there had been no complete transfer of cortical function to the striatum. The successful removal of both motor and "premotor" areas, and the integrity of the corpus striatum, had been verified after death. Richter and Hines (1938) have recorded, by means of an "activity cage," the spontaneous movement of five macaques before and after surgical injury to one or both frontal lobes. They report that unilateral ablations give rise to a notable increase in spontaneous activity only if the anterior poles of the caudate nucleus and putamen are involved. Bilateral lesions, however, are effective in this respect without complementary striatal insult. Langworthy and Richter (1939) obtained similar results in cats.

More recently Weisschedel and Jung (1938-9), and Jung and Weisschedel (1938) from Hess's laboratory, have made electrolytic lesions 1 to 5 mm. in diameter in the basal part of the brain in cats and obtained some results which are in some respects related to our own, though these authors were mainly concerned with the effect of their lesions upon the balancing mechanisms. Their lesions were not always small.

A preliminary report of our own experiments has been made to the Physiological Society (Liddell and Phillips, 1939).

Methods.

Forty-three have been used in this series. Of these, seven were intentional control experiments, and a further ten, in which electolytic lesions were placed in parts of the brain other than the basal ganglia, or were absent altogether, served also as controls. Female cats of approximately 2·5 kg. body-weight were chosen for observation, if of a friendly and docile character. Timid animals which resent examination are useless. The anæsthetic used was nembutal, 37 to 40 mgm. per kg. body-weight intraperitoneally. After incising the scalp with full aseptic care, and trephining an appropriate opening in the skull with a dental burr, the concentric needle electrodes (Adrian type) for electrolysis were guided into the desired region of the basal ganglia by use of the Souttar-Beattie stereotaxic apparatus. Beattie has found that with the head stirrup of this instrument inclined forward at an angle of 10° to the vertical, a needle carried vertically downwards through the external bregmatic point of the skull in female cats of 2·5 kg. body weight will pass through the middle of the optic chiasma when it reaches the base of the brain. In order, therefore, to place the tip of the needle at any desired point, it is only necessary to know the distance of that point (*a*) in front or behind the transverse bregmatic-chiasmatic plane, (*b*) lateral to the mid-line, and (*c*) below the plane at right-angles to the transverse bregmatic-chiasmatic plane and tangential to the external bregmatic point. The downward movement of the needle is controlled by a rack and pinion and measured on a millimetre scale with a vernier. The horizontal ranging of the needle is defined by attachment to a pantograph arm (2 : 1), moving over a measuring table.

It is important that the external surface of the electrode needle should be insulated with enamel, except at the tip, because if not, electrolysis will occur along the whole length of the shank, so that a seriously large needle track may be left in the brain substance. When, however, the needle has been enamelled, its track is found to be negligible.

For electrolysis, a current of 3 to 5 ma. is passed for two to five minutes from a 12 to 16 volt battery, through a variable resistance. In some preparations single, in others multiple lesions have been made. The lesions measure 1 to 2 mm. in diameter and 2 to 4 mm. in their long axis in the tissue fixed post mortem.

Representation of different regions of the basal ganglia in terms of distances along the three co-ordinates has been achieved by a simple method. The normal hemispheres of ten female cats 2·5 kg. body-weight have been fixed in situ in the calvarium by perfusion with warm physiological saline, followed by 5 per cent. formol-saline, the subjects having been first anæsthetized by nembutal. The shrinkage of brain tissue caused by this method is very slight: on the cerebral surface about 2½ per cent. linearly. When the brain is dissected out the level of the bregma is marked on each hemisphere by means of a fine pin. The brain is then divided sagittally with a brain knife and the medial surface of the hemisphere to be measured is blotted dry and laid off on squared paper. A vertical line is drawn to pass through the middle of the cut edge of the optic chiasma below and the bregmatic point above. The thickness of the bone, &c., intervening between the surface of the hemisphere and the external bregma (usually 2 to 3 mm.) is represented by the space between the top of the hemisphere and an appropriate horizontal line above. The contour of the hemisphere is dotted in. When, subsequently, the hemisphere is sliced into 2 mm. slabs, the depth of any point on the surface of a slab from the external bregmatic (tangential) plane will be given by its depth from the upper edge of the face (medial edge) plus the distance of this upper edge below the tangential plane, as read from the squared paper tracing. The hemisphere is next cut in two in the bregmatic-chiasmatic plane into rostral and caudal pieces. These are then sliced by a simple macrotome into 2 mm. slabs parallel to the bregmatic-chiasmatic plane. Four or five slabs are usually taken anterior to the plane, and eight posterior to it. They are then photographed serially, and from the photographs the measurements are made. It is found that agreement between homologous measurements in different brains is reasonably good. Such discrepancies as do exist are referable to slight antero-posterior variability in the position of the bregma relative to the brain.

Control injuries have been two kinds; in one series, the needle was passed into the brain substance without the subsequent passage of any current; in the second series, an area of the cortex at the anterior end of the sulcus lateralis, where it joins the sulcus ansatus (Winkler and Potter, 1914), was injured with an electrocautery. It is through this region that the electrodes pass on their way to the basal ganglia.

For the examination of tissues with lesions the same perfusion technique, as above, was employed, and the brain was removed after the immersion of the trephined skull in 5 per cent. formol-saline for at least twenty-four hours. The position of the lesions was determined either by the inspection of the gross 2 mm. slices, or of sections stained by Weigert's or Busch's method. Descending degeneration in the cerebral peduncles, medullary pyramids and spinal cord has been sought in Weigert or Busch preparations.

Results.

Control series.—The seventeen control experiments were all essentially negative. In seven of them the needle was passed into the basal ganglia,

but no current was passed. They showed no physical signs during survivals ranging from one to four weeks. Three further controls had circumscribed cortical lesions from the electrocautery, 5 to 10 mm. in diameter. In two of these, these lesions were placed at the junction of the sulcus lateralis and the sulcus ansatus, where the needle passes on its way to the basal ganglia. In the other, the lesion was placed at the lower end of the gyrus ectosylvius posterior, a field from which Tower (1936) has evoked both movement and its inhibition after section of the medullary pyramids. In a third group of controls, seven animals showed only very slight and variable signs from the lesions in the radiatio corporis callosi: in the olfactory tracts, gyri and pyriform area; and in the parietal cortex and corona radiata above and lateral to the basal ganglia.

Experimental series.—Twenty-six cats had lesions in various parts of the basal ganglia:—

Lenticular and caudate nuclei	1 cat
Caudate	4 cats
Bilateral lenticular	2 „
Unilateral lenticular	13 „
Subthalamic	2 „
Claustrum	4 „

All these animals presented a characteristic clinical picture. In keeping with the sudden onset of the cerebral injury—its "momentum," in Hughlings Jackson's[1] phrase—the physical signs are most severe during the days immediately following its infliction, but soon diminish, and later reach a steady state which is maintained for three months or more. This initial diminution is probably largely due to, and coincident with, reduction in surrounding œdema. To what extent if any "compensation" may enter into it is uncertain.

Physical signs.

(1) *Extensor hypertonia on the contralateral side.*—The leading sign is extensor rigidity in the contralateral limbs. The rigidity, if slight, is masked. To a superficial examination the gait may then seem normal, but when the animal is nursed on the observer's knee, or suspended comfortably with the limbs hanging freely (Langworthy, 1928; Bard and Rioch

[1] "In all cases of nervous disease we must endeavour to estimate most carefully the element of rapidity of lesions, not only the quantity of nervous elements destroyed, but the rapidity of their destruction. We have to try to estimate the momentum of lesions. . . . The slowness with which a lesion comes on is determined by the slow onset of the symptomatic conditions; a small sudden hæmorrhage produces greater but a more temporary effect . . . than a large, slowly developed softening." (1932, II, p. 196.)

1937; Liddell, 1938) the rigidity becomes clear. The contralateral hind limb is strongly protruded. Passive flexion imposed under such conditions on the hind-limbs with a spring dynamometer (Liddell, 1934, 1936) shows that the rigid limb, which is then stiffly extended, may need 2·5 to 3·0 kg. pressure to flex it, while the other (control) limb needs only 0·5 to 1·0 kg. and is not held extended. The rigidity is different from the classical decerebrate rigidity of Sherrington, in that "clasp-knife" collapse is absent. It offers solid resistance throughout the flexion phase. The forelimb and neck may also be rigid, the head being turned to the side of the lesion, but this is not invariable. Bilateral lenticular lesions (2 cats) caused bilateral extensor rigidity. Voluntary power of the limbs, as tested in struggling and the ability to scale the wire grill on the windows, is apparently unimpaired in the rigid muscles, at least when the animal is in the mood to struggle, but at other times, when the animal is feeling playful or less stressed, the normal limb is used in preference to the rigid limb.

(2) *Delayed flexor reflex on the contralateral side.*—The flexor reflex on the affected side is delayed and of high threshold. The toe is only withdrawn from a pinch *after* mewing, giving the impression that reflex withdrawal is delayed, and that the withdrawal is made by cerebral intermediation, after feeling the pinch.

(3) *Tactile placing reactions.*—Tactile placing reactions (Bard 1938) are deficient on the affected side; but for this the impairment of the motor mechanism, rather than any sensory or cortical disturbances, seems responsible.

(4) *Flexor hypertonia on the ipsilateral side.*—The state of the flexor muscles of the hind-limbs can be tested, as the cat lies supine and symmetrical and is petted on the lap of an assistant, by means of a couple of tension spring balances held by the observer. Each balance is attached by a wash-leather tie to the cat's ankle. The cat does not care for this procedure, and, as a rule, holds its ipsilateral hind-limb closely flexed, so that a force of 2 to 2·5 kg. may be needed to extend it. Extension by hand reveals a tremulous resistance—reminiscent of, but not necessarily related to, the cog-wheel phenomenon of Parkinsonism (Wilson, 1925, Lecture III). The contralateral limb, however, is held extended, or if forcibly flexed, needs only 0·5 kg. to extend it. This distribution of rigidity—ipsilateral flexor and contralateral extensor—is similar to that noticed by Bazett and Penfield (1922) in the chronic hemidecerebrate cat, though, as mentioned, in our cases the extensor rigidity at least is of different quality, in that it shows no clasp-knife effect. Langworthy (1928) has described a similar distribution in the hind-limbs of hemidecorticate cats.

(5) *Disuse of the eyelids.*—Sometimes the contralateral superior eyelid does not close properly, even if the cornea itself be touched, but the nictitating membrane is used freely instead. Conjunctivitis may be a sequel of the inability to close the eye. This condition usually passes off in seven to ten days.

(6) *Gait.*—In some cats the gait is not quite normal, there being a tendency to circle to the side of the lesion. Bilateral lesions produce a noticeably stiff gait. These animals walk in a rather stealthy crouching fashion.

(7) *Magnet reaction* (Magnus 1926).—The contralateral hind limb, after it has been forcibly flexed, shows this reaction, sometimes in the classical manner, at other times (and most frequently) haltingly and by stages. That is to say, the pad follows the observer's palm only for an inch or two and then stops. When the observer touches the pad again, the limb extends a little further more, and then stops. After four or five such stages, the limb at last reaches full extension. The reaction is not found on the ipsilateral side.

(8) *Sprungbereitschaft* (Magnus 1924).—This reaction is frequent in the contralateral hind limb. To show it, the animal is held by the scruff of the neck and rapidly lowered towards the floor. The contralateral limb shows, in that moment of lowering, an even greater degree of extension in knee, ankle and toes than does the ipsilateral limb.

In none of our preparations has there been any recovery from the concealed hypertonia, even after 128 days, nor, on the other hand, has there been any paralysis. There has only been some slight remission of the physical signs in the course of the first week, as already remarked. There has been no sign of spontaneous tremor or of other involuntary movements, even after bilateral striatal or unilateral subthalamic injury.

As an example, the protocol of one subject (No. 20) will be given:—

June 7, 1939: Wt. 2·5 kg. 2 lesions in the left lenticular nucleus; co-ordinates: (1) 2 mm. posterior to bregmatic-chiasmatic plane, 7 mm. to the left of mid-line, 21 mm. deep to bregmatic-level; (2) 4 mm. posterior, 10 to left, 22 mm. deep.

June 8: Fully recovered. Circles to right, pirouetting around stiffly extended right hind-limb, right eyelid immobile and nictitating membrane used. To forced flexion, (compression dynamometer), righ hind-limb offers 2·5 kg. resistance, left 1·0 kg. Delayed flexor reflex on the right.

June 10: Circles now to the left. Right hind-limb stiffly abducted during circling. Dynamometer, right 2·5 kg. to forced flexion, left 1·2 kg. Delayed flexor reflex on right. Out of doors, on the lawn, birds, &c., distracted her and circling not so marked.

June 13: Still circles vigorously to the left. Right superior eyelid does not close but nictitating membrane used freely, both spontaneously and when cornea touched.

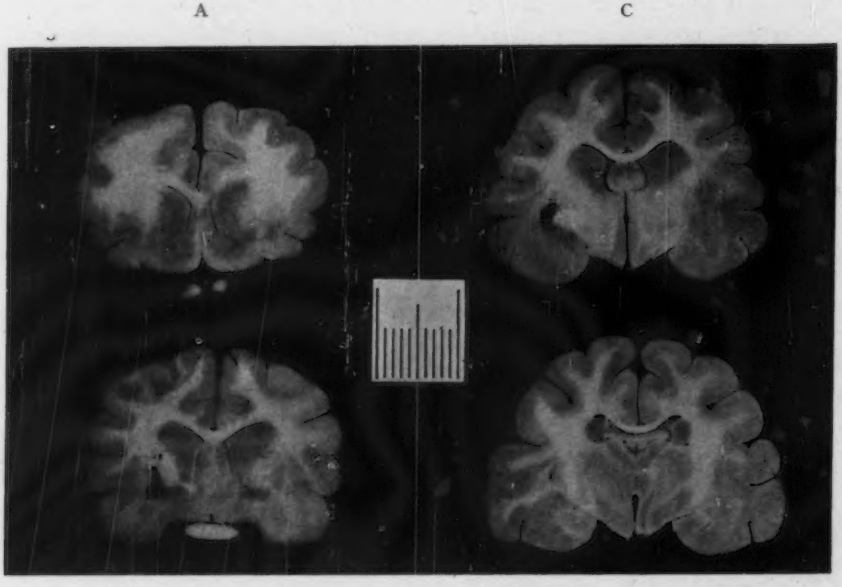
Left hind-limbs 1·0 kg., right 2·2 kg. to forced flexion. Right spontaneously extended.

June 20: Circles to the left, especially when first released from cage. Left hind-limb 2·5 kg., right 1·2 kg. to extension balances, which were resented on left. Compression dynamometer, left 1·4 kg., right 2·2 kg. head turned, chin to left, vertex to right. Right flexor reflex not delayed. In struggling, uses left foot more. Nictitating membrane sign absent.

July 8: Demonstrated to Physiological Society but frightened and difficult.

July 22: Still circles to left. Right hind-limb more extended and markedly delayed flexor reflex. 2·0 kg. needed for forced flexion, on left 1·0 kg. suffices. To extension balances left 2·5, right 1·5 and resented.

Nembutal; routine perfusion. *Post-mortem findings.*—Lesion limited to middle part of putamen just transgressing external capsule and involving claustrum. Injury is adjacent to internal capsule. No degeneration in spinal cord.



CAT No. 20.—2 mm. frontal slabs of fixed brain to display structures in the following planes of section: A, 2 mm. anterior to bregmatic-chiasmatic plane; B, actual level of bregmatic-chiasmatic plane; C, 2 mm. posterior to bregmatic-chiasmatic plane; D, 4 mm. posterior to bregmatic-chiasmatic plane. No injury is evident in A. A lesion in the left putamen is seen in B and C, and to a small extent in D. Scale in mm.

The results in other cases are tabulated briefly in the table (p. 271). From this preliminary series of experiments the finer points of difference in physical signs arising from differently localized basal lesions are now

being defined more accurately (Christensen). Although the signs vary somewhat from day to day, the figures quoted for the difference in hypertonia between the two hind-limbs are a fair sample of those readings themselves as well as being indicative of the presence of the other extrapyramidal signs which accompany the leading sign in more or less degree (pp. 267 to 269).

TABLE.

Lesion(s) of	Cat	Survival (days)	Needle track	Injury to internal capsule	Compression dynamometer readings in kg., contra-lateral limbs given first
Lenticular and caudate (unilateral) nuclei	1	79	++	+++	3·0 : 0·8–1·0
Caudate nucleus (unilateral)	2	24	0	0	1·6 : 0·8–1·0
	3	40	0	0	1·6–2·0 : 0·8–1·0
	4	104	+	0	1·5–2·5 : 0·8–1·0
	5	7	0	0	2·0–3·0 : 0·8–1·0
Lenticular nucleus (bilateral)	6	20	+	+	Both 2·5–3·0
	7	73	+	+	Both 2·5
Lenticular nucleus (unilateral)	8	76	+	+	1·5–2·0 : 0·8–1·4
	9	77	+	+	1·5–2·5 : 1·0
	10	127	0	0	Flexor reflex delayed in contralateral hind-limb. Ipsilateral flexor hypertonia
	11	120	+	++	2·5–3·0 : 1·0–1·5
	12	128	0	+	2·0–2·6 : 1·0–1·2
	13	Quadriceps de-afferented *ab initio*; on 70th day basal lesion made; killed on 146th day	+	++	De-afferented limb remained flaccid after basal lesion
	14	75	+	+	2·5–3·0 : 1·0–1·5
	15	81	+	+	1·5–1·8 : 1·0
	16	25	0	+	2·0–3·0 : 1·0–1·5
	17	91	0	0	Sign of nictitating membrane and delayed flexor reflex; latter permanent
	18	31	0	0	2·0–1·2 : 0·8
	19	49	0	++	2·5–1·5 : 1·0
	20	45	0	+ v. slight	2·0–2·5 : 1·0
Subthalamic region (unilateral)	21	63	+	Cerebral peduncle	2·5–3·0 : 1·0–2·0. Contralateral quadriceps de-afferented 23 days after brain lesion. Then for two weeks readings were 1·0–1·4 : 1·0–1·5, but later were 2·0–2·5 : 1·5–2·0
	22	42	+	peduncle	2·0–3·0 : 1·0. Contralateral quadriceps de-afferented 27 days after brain lesion. Then for ten days readings were 1·0 : 1·6
Claustrum (unilateral)	23	59	+	0	2·0–2·3 : 1·0–1·8
	24	23	+	0	Readings commonly equal
	25	64	0	0	3·0–1·5 : 1·5
	26	40	0	0	2·4–1·8 : 0·6

In two cases, symmetrical bilateral lesions were made but they did not produce any effects other than the usual effects, bilaterally. If there was any difference in degree in the signs between the two sides, that corresponded with slight accidental difference in the extent of the lesions (Cats 6 and 7).

De-afferentation.—Some preliminary experiments were done on the effect of de-afferentation. More than two months before making the basal lesion one animal (Cat 13; *see* Table) was prepared by de-afferentation of the knee extensor on one side. After the basal lesion had been made on the contralateral side, rigidity failed to appear in the de-afferented limb. The immediate effect of the second operation was the return of the incoordination which had originally followed the dorsal root section, but which had been completely compensated during the interval. Two weeks after the second operation, however, walking was almost normal again, though the affected limb continued to show flaccidity when examined by the usual methods. The knee extensors on one side of two other cats (21 and 22) were de-afferented twenty-three and twenty-seven days after the brain operation. The knees were rendered flaccid at first but, subsequently, some measure of tone was restored and the latest observations before the close showed that the affected limb might come to give readings higher than on the normal side.

Discussion.

The results obtained from these preliminary experiments on the placing of lesions 1 to 2 mm. in diameter and 2 to 4 mm. deep (*see* fig.) in basal ganglia has encouraged further work which is now in progress. From such lesions as we have made, there has followed hypertonia in the limbs. The "release" so documented is, when slight, masked by voluntary movements. Our experiments raise more questions than can, at present, be answered. What is the nature of the release? How small can the lesion be which gives this release? Is there any sort of localization? (Vogt and Vogt, 1920). Do our lesions injure only the extrapyramidal system and leave unharmed the pyramidal projections? To this last and important differentiation, we can answer that, even in our small series, the evidence points to the implication of the extrapyramidal system and not of the pyramidal system in the production of hypertonia. Such differentiation would be simple if pure pyramidal injuries in the cat did not produce any release of hypertonia. But section of a medullary pyramid (about the level of the olive) *does* result in hypertonia, at any rate for some weeks, though possibly not so permanently as even a small lesion in the extrapyramidal system. It is never so

severe (when unilateral) as to be even slightly disabling and needs care for its revelation. This release of hypertonia in cats by pyramid section, mentioned by Marshall (1934), and by Tower (1935), has been confirmed by one of us in this laboratory (Liddell, unpublished).

Hence, in the present series, one has to fall back on accurate placing of the lesion in a non-pyramidal region, arranging that the needle shall not pass through a pyramidal-region.

But further difficulties have to be watched, namely, the accidental injury of extracapsular pyramidal-fibres which may pass on their course directly through the basal ganglia and may be inextricably blended with them. If at all numerous, which usually they are not, their degenerated remains should have been detected in our examination of the spinal cord. Absence of any degeneration in the pyramidal tracts cannot, however, be taken in any circumstance as definite evidence of absent pyramidal activity, since fibres may be functionally impaired before they are anatomically degenerate. Any such control, therefore, would not be absolute, but it would indicate gross pyramidal deficiency if such were there. As stated, however, it has been absent and so we presume that there has been no gross injury of the pyramidal system.

The lesion in the basal ganglia, wherever it may be, is readily defined at examination post-mortem, by methods already described and there is, in the cord, no sign of degenerating fibres. Hence we believe that our lesions are specific lesions of various loci in the basal ganglia, and that the hypertonia of particular muscle-groups which follow those lesions in its various aspects is the definite result of those lesions, and not of the very slight incidental damage produced by the track of the needle.

Although lesions in these preliminary experiments have been placed in widely separated regions in the basal ganglia, we do not now present any evidence of precise localisation of function. The manifestation of lesion is, broadly speaking, the same in all cases, whatever the site, and that manifestation is, in the main, hypertonia of limb musculature. But a further account, in greater detail, of the effects of such lesions will be published by Christensen.

SUMMARY.

(1) Electrolytic lesions have been made in the basal ganglia of cats, twenty-six in number.

(2) The leading physical sign of such lesions is slight but persistent hypertonia of extensor muscles in the contralateral limbs. The hypertonia is not evident in the gait, and does not become so unless the animal is mentally at rest, and is held up so that the limbs hang freely.

(3) Other physical signs are: (i) Delayed flexor reflex; (ii) defective placing reactions; (iii) flexor hypertonia on the ipsilateral side; (iv) defective closure of the contralateral eyelid.

(4) De-afferentation appears to give some temporary reduction of the extensive hypertonia.

(5) Control experiments consisting of the passage of electrodes into the basal ganglia without electrolysis (7 in number) and of lesions elsewhere than in the basal ganglia (10 in number) were unproductive of permanent physical signs.

We have to thank Professor John Beattie, of the Royal College of Surgeons, for facilities in his laboratory at the beginning of our experiments, as well as for his help in the use of his stereotaxic instrument. We have also to thank the Christopher Welch Trustees for purchasing a stereotaxic instrument for the Oxford laboratory.

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FAMILIAL PES CAVUS AND ABSENT TENDON-JERKS: ITS RELATIONSHIP WITH FRIEDREICH'S DISEASE AND PERONEAL MUSCULAR ATROPHY.

BY JOHN D. SPILLANE,

THE group of heredo-familial disorders characterized by degeneration of cerebral, spinal and cerebellar pathways has not, as yet, received any satisfactory classification based on pathological evidence. The rarity of many forms makes a comprehensive study difficult and few observers can personally examine sufficient material. Clinical descriptions often vary and can be misleading, while rudimentary and intermediary forms add confusion. Again, the "classical" clinical description may be uncommon or later prove to be incomplete. Friedreich (1861), for example, did not allude to the characteristic foot deformity in his account of the malady that now bears his name. To Charcot belongs this credit.

On the pathological side it may be recalled that several of Marie's original cases of "hérédo-ataxie-cérébelleuse" later proved to have pathological lesions of various kinds. Marie's conception of a "cerebellar atrophy" as the basis of the disorder was incorrect.

It is thus apparent that clinical studies alone cannot lead to the final classification of these disorders, but they may, if accurate and reliable, materially aid in the recognition of the more clear-cut varieties. With the clinical study of one recently described familial syndrome this paper is concerned.

In 1926 Roussy and Lévy described a heredo-familial affection which they believed to be hitherto unrecorded. Briefly, it was characterized by bilateral pes cavus, absent tendon-jerks, difficulty in walking, clumsiness of the hands with, in some cases, slight wasting of the thenar and hypothenar eminences. On the negative side, kyphoscoliosis, sensory changes, extensor plantar responses and typical cerebellar signs such as nystagmus, disturbances of speech and involuntary movements, were absent. The disease began in infancy and first showed itself by a delay in learning to walk, by clumsiness and frequent falls. The foot deformity was noticed early and developed during childhood. Running, jumping and participation in school games eventually became impossible. Thereafter, the disease failed to progress and in adult life gait and equilibrium appeared

somewhat restored. Pes cavus, absent tendon reflexes and a certain amount of unsteadiness of the legs, however, remained. The authors personally observed seven members of a family with this disease and traced its inheritance through four generations. Several other members were known to be similarly affected. In 1932 and again in 1934 they reviewed the problem in the light of additional reports and concluded that they were justified in regarding it as a hitherto undescribed clinical syndrome for which they proposed the term "Dystasie aréflexique héréditaire."

In the year of their original report there appeared two other papers describing similar patients. Symonds and Shaw (1926) entitled their paper "Familial Claw Foot with Absent Tendon-jerks; a 'Forme-Fruste' of the Charcot-Marie-Tooth Disease." They observed ten members of a family with similar clinical features and showed its inheritance through three generations. Bilateral pes cavus was present in each affected member and the tendon-jerks of both upper and lower limbs were either absent or markedly diminished. Slight atrophy of the intrinsic muscles of the hands was observed in four patients and in the peroneal group in one other. In two patients the electrical muscle reactions were diminished. No evidence of cerebellar involvement was detected and the cases were considered identical with those described by Roussy and Lévy. Symonds and Shaw, however, came to the opinion that they represented a "Forme-Fruste" of the peroneal muscular atrophy of Charcot-Marie-Tooth.

Rombold and Riley (1926), on the other hand, considered their group of patients to be suffering from an abortive type of Friedreich's disease. They observed bilateral pes cavus and absent tendon-jerks in eight members of a family through three generations. Again, cerebellar signs and sensory changes were absent. Roussy and Lévy, commenting on these case reports, included them in their syndrome.

Popow (1932) published an account of a family with nine affected members, all males, in four generations. Bilateral pes cavus and absent tendon-jerks were observed in all. No signs of cerebellar disease were present and the patients resembled those of Roussy and Lévy in all respects save for a dorsal kyphoscoliosis in one. Popow agreed with the latter that the disease differed from both Friedreich's disease and the Charcot-Marie-Tooth disease and that it constituted a new clinical syndrome; he suggested the term "Héréditaire paréto-incoordination syndrome."

Van Bogaert and Borremans (1932) presented their observations before the Société de Neurologie de Paris. They studied the condition in eight members of a family in three generations and noted the pes cavus, the

tendon areflexia, the absence of cerebellar signs and of any sensory abnormalities. In addition, however, they observed a kyphoscoliosis in four of their cases and a gross lordosis in one other. A certain degree of arrested mental development was also present in one patient. They concluded that the disease could be regarded as a separate condition, differing from Friedreich's disease and from Charcot-Marie-Tooth's disease. They raised the question of the possible separate, hereditary transmission of the kyphoscoliosis factor.

Darré, Mollaret and Landowski (1933) described an isolated example of the disorder with pes cavus, absent tendon-jerks and without any signs of cerebellar or sensory involvement. The parents and relatives of the patient, a girl aged 10, were unaffected. One other child had died of meningitis in infancy. There was some evidence of diminution of labyrinthine functions and chronaxie measurements were abnormal; findings which suggested to the authors a relationship with Friedreich's disease.

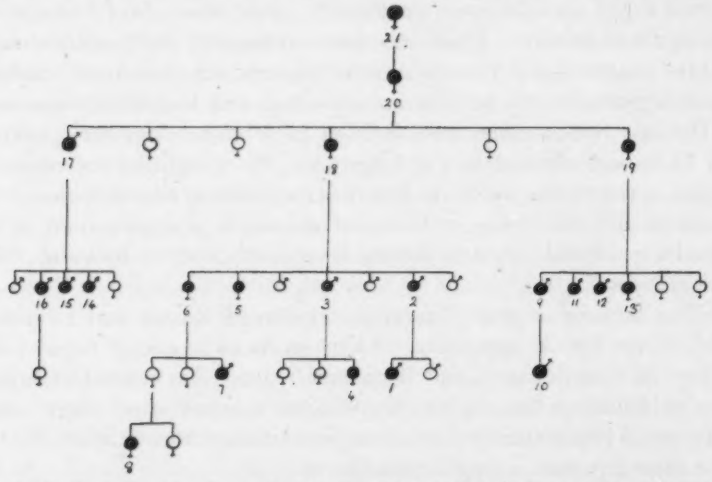
Dimitri (1935) studied the condition in a brother and sister aged 15 and 12 respectively and in a girl aged 16. He recognized the relatively benign course of the condition and the characteristic foot deformity. He conceived the underlying pathological process as a degeneration of the posterior roots and columns, linking it with the abortive forms of Friedreich's disease.

Thus far, the original clinical description of Roussy and Lévy held good, except for the appearance of kyphoscoliosis in one of Popow's and in four of Van Bogaert's and Borremans' cases. But reports have since been published of cases in which additional symptoms have been noted. They are of importance in view of the contention of Roussy and Lévy that their cases represent a separate syndrome.

Gordon (1933) met with four individuals of a family, in three generations, in which a right-sided scapulo-humeral atrophy was associated, in three of them, with the features of the Roussy-Lévy syndrome. There were generalized tendon areflexia, double foot drop with valgus deformity and the "Friedreich" position of the great toes. The gait was of a steppage type in all three, while two had, in addition, a scoliosis. Speech disorders, involuntary movements, nystagmus and other cerebellar signs were absent.

Sterling (1933) observed the syndrome in a woman, aged 45, who had suffered from migraine attacks for many years and from a profound depressive state with character changes and cataplexy for three years. Her only child, a girl aged 13, had a total abolition of all tendon reflexes. No mention was made of the existence or otherwise of pes cavus in this

child. Giraud and Derombies (1934) followed with an account of the syndrome in a boy aged 17 with pronounced personality changes and maniacal outbursts that necessitated certification. His mother and maternal grandfather also had bilateral pes cavus and absent tendon-jerks. Giraud and Ajuriaguerra (1934) described a case in which bilateral pes cavus and tendon areflexia were associated with an Arran-Duchenne type of muscular atrophy, with Argyll-Robertson pupils and pronounced temperamental instability. Delusions of persecution and an attempt at suicide led to his certification. No clinical or serological evidence of syphilis was forthcoming. There was abolition of all tendon reflexes in the patient's mother. No mention was made of other members. Finally, Mollaret



Family Pedigree; affected members indicated by black symbols. Numbers below symbols refer to case numbers in text. Case 4 is an example of Friedreich's disease. Cases 9, 19 and probably 20 are typical cases of Charcot-Marie-Tooth muscular atrophy. Cases 1, 4, 7, 11 and 12 have an explosive type of dysarthria in addition to the features of the Roussy-Lévy syndrome.

and Cachin (1934) observed a brother and sister with bilateral pes cavus and tendon areflexia, both of whom suffered from severe, lightning-like pains in the lower limbs. Bilateral optic atrophy was present in both, with marked reduction of senses of position and vibration. The pains could only be controlled by morphine and both patients subsequently became morphomaniacs. Cerebellar signs were absent. The remainder of the family were normal, but ten brothers and sisters had died in childhood of diverse conditions. The authors believed these cases represented a

posterior root-column type of Friedreich's disease analogous to those of Roussy and Lévy.

It is now proposed to add to the review of the literature on this subject an account of an affected family recently studied by the author. The disease was probably present in six generations, affecting twenty-one members (see above).

Case 1.—The original patient in this series was a Jewish youth, aged 18, a private in the British Army. He sought advice at a Military Hospital about his feet. He said he suffered from "the family complaint," which he described as "bad feet and clumsy gait," and complained that he could not do the marching and standing expected of him. He spoke with a stutter and in short bursts. Inquiry showed that no deformity was present at birth but that attempts at walking —at about one year of age—failed completely. He fell continually and during his second year seemed quite unable to acquire any control of his legs. He was unable to take his first steps unassisted till the age of 4 years. At about this time his father first recognized that the child was developing the short, high-arched, stumpy foot that characterized so many of his family. The patient was also slow in learning to talk and speech always remained indistinct and difficult, although some improvement was alleged to take place after many courses of treatment during school years. He developed normally in every other way but his clumsy legs prevented him from running, jumping and taking part in any school games. Advice was sought at several clinics and massage, exercises and plaster casings for his feet were in turn tried. Operative interference was discouraged by relatives who had received no aid from various orthopædic procedures. At puberty the deformity seemed well-established, the toes showed a decided tendency to curl up and he walked on a rather wide base, lifting his legs well from the ground. Our patient, an unusually intelligent and observant subject, offered information which he, with some other members of his family, had observed regarding their disability.

Firstly, affected members were quite unable to jump more than three or four inches off the ground, although power in their legs was good as a whole. Secondly, mounting steps or stairs always entailed exceptional effort; the toes readily catching in the steps. Thirdly, and rather remarkably, several of them had noticed that their knee-jerks were absent. In the majority this occurred in childhood and before any attention was drawn to the subject by medical men during examinations for insurance policies. As children, several of them had entertained unaffected relatives and friends with this peculiarity. Finally, they were aware that an affected person when raising himself from the kneeling position on the ground, always did so, not by placing the hands, palms downward, on the ground for assistance, but by closing the fists and pressing the knuckles into the ground. The patient's father informed me that his mother, who was herself afflicted, had often remarked on this peculiarity and said that it was noticeable from early childhood. The father himself thought it was due to a feeling of weakness and insecurity at the wrists in such a position.

Our patient joined the Territorial Army in 1939 hoping to find a post where his weak legs would not embarrass him. For a time he was successful, but new duties, incurred after War broke out, soon led to much deterioration in his foot condition. He grew more incapacitated and was finally discharged as unfit for service.

Examination.—Well-developed youth, tall and with long slender muscles. Heart and lungs normal. Cranial nerves normal, with the possible exception of diminished

FIG. 1.

FIG. 2.

corneal reflexes. No nystagmus, no palatal or pharyngeal paralysis. Speech was alternately clear and slurred; at times it became rapid, indistinct and "explosive." He appeared to have some control of this difficulty but certain consonants were consistently slurred. His spine was straight and normal. The pectoral, biceps, triceps and supinator reflexes were completely absent on both sides. There was no gross weakness or wasting of any of the muscles of the upper limbs, but there was a definite, albeit slight, flattening of the thenar and hypothenar eminences. The interossei were unaffected. There was neither fibrillation nor sensory change. Abdominal reflexes were brisk and equal. Both knee and ankle jerks were absent and the plantar reflexes were flexor on both sides. It was particularly noted that the sense of position was but slightly disturbed and that of vibration was normal. Rombergism was absent. There was some weakness of the extensor muscles of the feet and some generalized thinning of the peroneal group—without actual wasting. Both feet were high-arched, short and stumpy; the toes were rather *en griffe* and appeared to spring from the dorsal aspect and not the end of the foot. The curving inner margin of the foot was most apparent in the dependent position (fig. 1), while some readjustment took place under the weight of the body (fig. 2). Cerebellar signs were

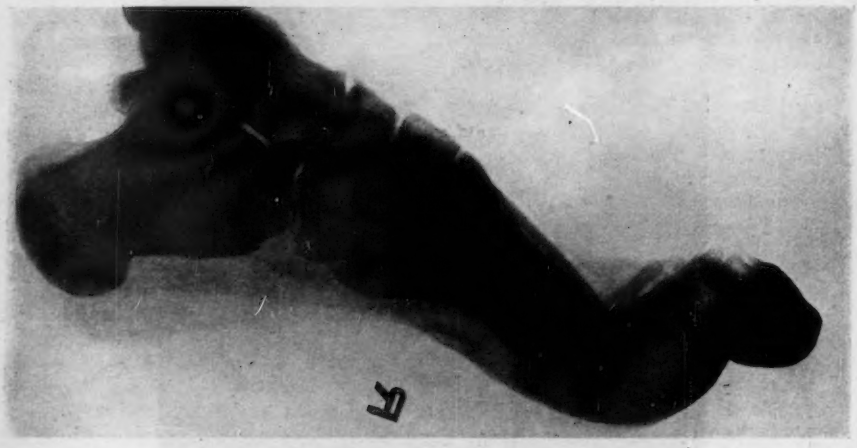


FIG. 3.

absent. Slight tremor of the outstretched hands was detected together with a certain clumsiness of the fingers when executing fine movements, such as doing up buttons, tying a knot or adjusting a tie. The patient could stand on one leg only with difficulty. Gait was awkward and slightly "steppage" in character with a wider base than normal. No bony deformity of the feet existed (fig. 3). Radiographs of the skull and spine were normal. Blood-count was normal. Wassermann and Kahn reactions of blood and cerebrospinal fluid were negative. The fluid was clear, colourless, under normal pressure, with cells 2 per c.mm. (lymphocytes), globulin increased, protein 110 mgm. per cent., chlorides 680 mgm. per cent., sugar decreased and Lange curve 0000000000.

Case 2.—Male, aged 50, father of the above patient. He has a moderate degree of bilateral pes cavus (fig. 4), complete tendon areflexia, with flattening of the thenar eminences. The remaining intrinsic muscles of the hands are normally developed. He cannot stand on one leg very successfully nor jump more than two or three inches in the air. His gait is relatively normal but on mounting stairs he betrays some awkwardness and instability. There are no cerebellar signs, no nystagmus or speech defect. During the Great War 1914-1918 he served as a transport driver, but always had to carry a small box around with him to enable him to climb into his seat. He was invalided out on account of "bad feet" in 1917.

FIG. 4.

Case 3.—Male, aged 55, brother of the above patient. He enjoys good general health except for occasional asthmatic attacks, but has a similar degree of bilateral pes cavus. Tendon reflexes are completely absent in upper and lower limbs. There is no atrophy of any muscles, but a detectable degree of weakness of the foot extensors is present on both sides. Plantar reflexes are normal. Speech is normal, sensation in all forms is intact, and there are no cerebellar signs.

Case 4.—Female, aged 18, youngest child of the above patient. Normal at

birth but showed difficulty in walking from an early age and a general clumsiness. The feet were normal in appearance at first but during the second year of life they were noticed to turn in and flop awkwardly on walking. At about 4 years of age her spine was noticeably kyphotic and difficulty in holding herself upright became apparent. She did not go to school and walking became more difficult. At the age of 14 she was admitted to hospital where bilateral club feet and a marked kyphoscoliosis were recorded. She was fitted with a spinal jacket. She now has an explosive type of dysarthria and is quite unable to walk without crutches. On attempting to stand unsupported she sways and falls. Club feet, absent tendon-jerks, extensor plantar reflexes, sluggish abdominal reflexes and the spinal deformity complete the picture of Friedreich's disease. Nystagmus and choreic movements are not present. The muscles of the limbs especially those of the legs are weak and wasted, but there is no localized atrophy. Indefinite blunting of sensation was found over both feet and lower third of each leg.

Case 5.—Female, aged 35, sister of patients 2 and 3. She has the typical foot deformity, with early clawing of the toes and weakness of the extensors of the feet. The calf muscles are thin but do not show any actual atrophy. Tendon reflexes are completely absent in arms and legs, and the plantar reflexes are normal. Her gait is normal despite the condition of the feet but she cannot walk far and tires rapidly. There is no Rombergism. There is no atrophy of the muscles of the hands and forearms but the grip is weak and fine movements of the hands are poorly performed. There is a tremor of both hands but no inco-ordination. Speech is normal and cerebellar signs are absent. There are no sensory changes.

Case 6.—Female, aged 40, sister of above patient. She shows identical foot deformity and absent reflexes, the pes cavus is more marked in the right leg and the great toe has been amputated on that side. Gait is fair, speech normal and there are no signs of cerebellar involvement. Callosities are present over most toes. There is no flattening of the intrinsic hand muscles but the grip is weak and a tremor of the hands interferes with the execution of fine movements. She has three children, one of whom, a male (Case 7) is afflicted.

Case 7.—Male, aged 20. He presents the triad of signs shown by his cousin, Case 1—bilateral pes cavus, absent tendon reflexes and speech defect. There is slight wasting of the thenar and hypothenar eminences and a certain amount of clumsiness of the fingers in the execution of fine movements. The peroneal muscles are not wasted but are rather weak; the remaining calf muscles are normal in development and strength. There is a doubtful Babinski sign on the right side; on the left side the plantar reflex is normal. There is no nystagmus. The speech defect is similar in all respects to that of his cousin. It is explosive, indistinct and accompanied by grimacing at times. He has received treatment for "stuttering" and has apparently shown some improvement in recent years. Gait is clumsy, while running and jumping are impossible. He shows the characteristic family difficulty in rising from his knees to the upright position; his wrists tend to give way on such occasions.

Case 8.—Female, aged 2, niece of the above patient. Weakness of the legs was noticed during the first year of life. The infant could not stand supported at the end of the first year, and the feet were noticed to drop readily. During the second year the feet assumed an equino-varus position and irons were procured. At the present time she can walk short distances and is said to be improving. The knee and ankle jerks are absent but the tendon reflexes of the arms are present although markedly diminished. Speech appears to be developing normally and no cerebellar signs could be elicited.

This patient's mother has not been examined and is reputed to be quite unaffected. Her husband informed me, however, that her feet "are not strong."

Case 9.—Male aged 32. This man presents all the signs of a well-established Charcot-Marie-Tooth atrophy. He was late in learning to walk, was never able to run and join in school games and has shown the characteristic foot deformity since childhood. Little success followed tendon operations on his feet, and he now has a well-developed degree of bilateral pes cavus with complete tendon areflexia in upper and lower limbs. There is atrophy of the calf muscles and of the lower segment of the thighs. The intrinsic hand muscles are wasted, with a main *en griffe* deformity, and a corresponding weakness of grasp. The muscles of both forearms are atrophied. The plantar reflexes are equivocal. The sensation of touch is unaffected but that of pain is considerably diminished over the distal segments of legs and arms. Vibration sense is absent below the knees. No fibrillation was observed. There is a fine tremor of both hands and fine movements of hands and fingers are impossible. Gait is clumsy and of a steppage type with a wide base. Speech is normal and cerebellar signs are completely absent. No Rombergism. The patient has recently been discharged from the Army with a diagnosis of Charcot-Marie-Tooth muscular atrophy. The mother (Case 19) tells me that her son's condition is similar in all respects to that of his maternal grandmother (Case 20).

Case 10.—Male, aged 4, only child of the above patient. Normal growth and intelligence, but was unable to walk until 2 years of age. He is now unsteady on his feet, walks on a wide base and cannot run or climb stairs. When placed on the ground in a sitting position he has great difficulty in getting up. The feet are normal although the arches are high. Tendon-jerks are completely absent. Speech is normal, there is no obvious localized muscular weakness or wasting, and cerebellar signs are absent. He thus presents the signs observed in our original patient and only further observation will tell us whether he will progress a further stage and, with his father and grandmother, eventually develop the complete picture of Charcot-Marie-Tooth muscular atrophy.

Cases 11 *and* 12.—Males, aged 30 and 28, respectively. These brothers of Case 9 have not been seen, but have undoubtedly a slighter form of the disease. They enjoy good general health, but have suffered great disability from their high-arched feet; like their brother they were taken to various orthopædic centres when children and tendon operations were perfomed: There is apparently no clawing of the toes, no muscular weakness, and no involvement of the hands. They both walk well, but cannot run far or jump. One of them is at present serving in the Navy; the other is a successful swimmer. Both men, however, have a speech defect, which is said to resemble that observed in their cousin Case 1. Corrective treatment has been unsuccessful.

Case 13.—Female, aged 25, sister of the above patients. She is quite normal in every way but the tendon reflexes of both lower limbs are completely absent. Plantar reflexes are normal. The feet are normal, but share the family tendency to be short, stumpy and high-arched. She walks and runs well and showed no delay in learning to walk as an infant. Speech is normal.

Cases 14, 15 *and* 16.—Males, aged roughly 40, 42 and 45, respectively. These men have not been personally observed but all have had difficulty with their feet, which are apparently typical of the rest of the family, and operations have been performed on all at some time or other. They are not grossly affected, but have never played games and cannot run well. It is not known whether the knee and ankle jerks are absent, but from the evidence of their aunt (Case 19), who is the family authority on the ailment, they undoubtedly have the same condition. Speech, intelligence, and the condition of the hands are good in all.

Case 17.—Male, aged 63, father of the above men. He has not been interviewed and is reputed to be strong and healthy with the exception of slight disability result-

ing from "the family feet." There is no apparent weakness or wasting of the legs but he has always been clumsy and unable to run and jump. Speech is normal.

Case 18.—Female, died at the age of 76 of a "stroke." She is said to have had the typical foot deformity to a marked degree and was unable to walk but short distances during her lifetime. Her sister (Case 19) informs me that her feet were clumsy and that the toes curled up. She could never run or jump. The legs did not waste; she remained stout and relatively strong until her death. Her hands were apparently normal. Speech was not affected.

Case 19.—Female, aged 62, sister of the above. She presents the symptoms and signs of a fully fledged picture of Charcot-Marie-Tooth muscular atrophy. She is an exceedingly intelligent and observant woman who has personally watched nearly every member of the family now alive for signs of approaching weakness of the legs and feet. She has bilateral pes cavus to a high degree and several toes have been amputated for painful callosities and progressive deformity. The peroneal group of muscles are atrophied although to a slighter degree than that seen in her son (Case 9). The thighs are unaffected; knee and ankle jerks are quite absent. There is definite atrophy of the intrinsic muscles of the hands and the forearms are slightly affected. All forms of sensibility, excluding heat and cold, are diminished over the hands and feet. Speech is normal and cerebellar signs are absent. Walking has always been difficult but her hands were not affected till the age of 40 or so. The disability has progressed almost imperceptibly all her life. She assures me that, from her observations of members of four generations of her family, it is impossible to be sure whether any member with the foot deformity in youth will or will not develop weakness and wasting of the legs and hands in later life. She has advised her children never to marry and the present difficulties shown by her grandson (Case 10) have been prophesied by her. The speech difficulties of some members have prompted her to add warnings of "brain disease and idiocy" in future generations. Observations which are pertinent and remarkable.

Case 20.—Little is known of this woman, but the evidence of her daughter (Case 19) strongly suggests that she was afflicted. The former recalls that her feet were deformed and that she walked awkwardly. Her hands were normal and speech remained unaffected. For the last few years of her life she could not walk or stand and remained bedridden. The cause of death is not known.

Case 21.—Evidence here rests only on the statements of patient 19. The latter informs me that she was always told that her grandmother had paralysis of the legs for many years. She has always understood that her mother's affection was similar.

Discussion.

The problem with which we are concerned involves the elucidation and classification of an alleged new syndrome. In this respect it is well to recall the arbitrary character of any classical clinical picture. The use of the terms "Friedreich's disease" and "Charcot-Marie-Tooth's disease" illustrates this point. Such designations are artificial in that they refer only to a selected group of symptoms and signs produced by a bigger underlying pathological process. It is this process alone which can truly be called a "disease." It is therefore obvious that the only genuine classification must be pathological, the latter term used in its broader sense and implying a full knowledge of ætiology. This is especially true of the

heredofamilial group of disorders of the nervous system. Here, the numerous and varying clinical pictures encountered reflect the sites and combinations of the morbid processes rather than their specific character.

On the other hand, failure to judge the accuracy of an original clinical report has before now led to delay in the recognition of a new disease. Such was the case when Friedreich (1861) published his account of hereditary ataxy. For twenty years the disease was considered by many to be an hereditary form of tabes dorsalis, but insistence by Friedreich and the eventual discovery, in 1884, of a case by Charcot at the Salpêtrière finally led to its recognition. These general remarks have some bearing on the problem of the syndrome described by Roussy and Lévy. These authors considered that Friedreich's disease could be excluded by the absence of cerebellar and pyramidal signs. Nystagmus, speech defects, hypotonia, involuntary movements and extensor plantar reflexes were not encountered. They were also persuaded that the absence of any definite muscular atrophy and of sensory and vasomotor changes made a diagnosis of Charcot-Marie-Tooth's disease improbable. In support of their belief in the individual character of the condition they stressed the constancy of the clinical history and signs in their own patients and in those of others. There were always present the difficulty in learning to walk, the unsteady gait, the inability to run and jump. Later in life the progress of the disease slackened and the gait improved, but the foot deformity was irreversible and the tendon-jerks remained absent. In childhood the ataxy and in adult life the deformity of the feet were the disabling features. Roussy and Lévy gained the impression that some functional adaptation developed as the child grew up. This characteristic feature they summarized as "régressivité dans l'enfance et fixité chez l'adulte." Popow thought that in childhood the condition was similar to Friedreich's disease while in the adult it resembled the muscular atrophy of Charcot-Marie-Tooth. The close similarity of the clinical features in succeeding generations seemed to point to the individuality of the malady. Furthermore, the absence of any other form of nervous disease, especially of abortive or complete forms of Friedreich's disease or peroneal muscular atrophy in the families concerned, lent support to this view.

However, such argument was weakened by the publication of reports, mentioned earlier in this paper, in which additional features such as kyphoscoliosis, mental deterioration and localized muscular atrophies were also observed. But it should be added that in those reports where mental changes were described the heredofamilial features were not closely investigated.

In our own series there were, in addition to sixteen examples of the syndrome as originally described, three instances of the complete picture of Charcot-Marie-Tooth muscular atrophy (Cases 9, 19 and 20) and one of Friedreich's disease (Case 4). Five affected members also had a speech defect (Cases 1, 4, 7, 11 and 12). No instance of an isolated speech defect was encountered. Two of the patients with the atrophy of the Charcot-Marie-Tooth type presented a classical picture of the disease; the third (Case 20) was not personally observed but witnesses affirm that here disability was precisely similar. In Case 4, in addition to pes cavus, absent tendon-jerks and disturbance of speech, the existence of a gross spinal deformity with bilateral extensor plantar reflexes made a diagnosis of Friedreich's disease almost certain. Nystagmus and involuntary movements were absent, but there was a greater degree of muscular weakness and inco-ordination than in the others.

In the whole family group, therefore, we have a clear indication that a relationship exists between the syndrome recorded by Roussy and Lévy and the disease processes described by Friedreich and by Charcot-Marie-Tooth. The existence of the three diseases in the same family could not be otherwise interpreted. Even in the absence of the Friedreich patient the presence of an explosive type of dysarthria in four other affected individuals would suggest the involvement of cerebellar pathways by the pathological process and hence the connection with Friedreich's disease.

The speech defect was similar in all personally examined affected members. Speech was jerky, slurred and the volume of sound poorly controlled, giving it an explosive character. Consonants were faultily pronounced as were the vowels also, but to a lesser degree. Fatigue aggravated the disability and overplay of the facial muscles, with grimacing, then appeared. No staccato effect was noticeable. The defect did not seem to resemble that recently described by Critchley (1939) in cases of cerebellar disorder; the fault lay with articulation and not with phonation.

There are few diseases which begin with pes cavus—Friedreich's disease, Charcot-Marie-Tooth's disease and a condition occasionally described as isolated familial pes cavus. In other families at present under observation I have noticed that unilateral pes cavus may be the only sign for many years of a heredofamilial nervous disorder and that in later life progressive muscular atrophy or peroneal atrophy may appear on the affected side. Many authors have drawn attention to the existence of abortive, intermediate forms, or " formes fruste " of these maladies, especially of Friedreich's disease (Tressider, 1893; Gladstone, 1899; Mingazzini and Perusini, 1904: Raymond, 1905; Armand Delille and Feuillée, 1909;

Elliott, 1913; Babonneix and Roederer, 1913; Farnell, 1916; Grenet and Ducroquet, 1927; Mollaret, 1929; and Wilson, 1940). A characteristic feature of these types has usually been their variability and their bizarre signs. Transmission in unchanging form is exceptional, while instances of the full-fledged syndrome have usually been found elsewhere in the family tree. Such observations led Marie to conclude that each family has its own interpretation of Friedreich's disease. A significant type of "forme fruste" of the latter is that consisting of absent knee and ankle jerks with or without some degree of pes cavus and difficulties of gait. Such cases seem to be identical with those of Roussy and Lévy. Amyotrophy, according to Wilson, is of frequent occurrence in Friedreich's disease (Rook, 1890; Bramwell, 1893; Hodge, 1897; Whyte, 1898; Jendrassik, 1902; Bing, 1905; Greenfield, 1911 and Biemond, 1928). The muscular atrophy may conform to any of the well-known clinical types. The co-existence of an atrophy of the Charcot-Marie-Tooth type and Friedreich's disease has actually been observed in the same individual (Greenfield, 1911), while the association of the two diseases in the same family has been noted by Spiller, 1910, Galliotti, 1928, and Biemond, 1928.

There is thus ample clinical evidence that the more clear-cut varieties in the heredofamilial disorders are in reality only the "high-lights" in a wider and more obscure background of neuropathy. The condition described by Roussy and Lévy and which was thought by them to be a distinct entity may be independently inherited, but this, in itself, is no guarantee of its individuality. The constancy of the clinical picture, nevertheless, does suggest that it represents a sub-group of the heredofamilial degenerations of the spinal cord and cerebellum which should be recognized. In its usually benign course it differs from Friedreich's disease and the muscular atrophy of Charcot-Marie-Tooth but further studies will be necessary to confirm this and to define its relationship with these conditions.

Summary.

A clinical study of the syndrome recorded by Roussy and Lévy has been made in a family in which members of five and probably six generations were affected. As originally described, the syndrome consists of bilateral pes cavus, absent tendon-jerks and some difficulty in walking and was thought to be a separate heredofamilial entity. Clumsy movements of the hands and flattening of the thenar and hypothenar eminences were inconstant while sensory changes and cerebellar signs were absent. In more recent accounts these findings and the heredofamilial nature of the

condition were confirmed but kyphoscoliosis and occasionally mental deterioration were observed. In one report also a unilateral scapulo-humeral atrophy was present in each case.

In the present study of one family group in which twenty-one individuals showed signs of spinal degeneration, there were sixteen instances of the syndrome, in four of which an explosive type of dysarthria was also present. The classical clinical picture of Charcot-Marie-Tooth's disease was observed in two patients and was believed to be present in a third. Another case was a fairly typical example of Friedreich's disease; this patient showed marked kyphoscoliosis, bilateral pes cavus, absent knee and ankle jerks and extensor plantar reflexes. Nystagmus and involuntary movements were absent.

In the absence of pathological evidence it is concluded that the syndrome of Roussy and Lévy represents a sub-group of the heredofamilial degenerations of the spinal cord and cerebellum of which Friedreich's disease and the muscular atrophy of Charcot-Marie-Tooth are fully fledged examples. It is an intermediate and abortive form but because of its tendency to regression and to transmission in a more or less constant fashion it is worthy of recognition.

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Notices of Recent Publications.

The Hypothalamus and Central Levels of Autonomic Function. Research Publications, Vol. XX, of the Association for Research in Nervous and Mental Disease. Baltimore: Williams and Wilkins Co. 1940. Pp. 980. Price 10 dollars.

This is perhaps the most ambitious and comprehensive statement of hypothalamic anatomy, physiology and pathology hitherto published and it will for some time remain a principal work of reference for workers on the subject, and for those who seek a statement of our present knowledge.

Not the least valuable chapter in the volume is that giving what it may be hoped will be a standard terminology for the hypothalamus, pre-optic region and hypophysis.

The clinical application of the vast mass of information contained and summarized in this volume is yet far from complete, as also is the interpretation in terms of hypothalamic physiology of many clinically observed symptoms now somewhat facilely attributed to disorders of the hypothalamic-hypophysial mechanism. Hence it is that Part III, a clinical symposium of the hypothalamus, is at once the shortest and the least precise component of this volume.

Diseases of the Brain. By W. Russell Brain. London: Oxford Medical Publications. 1940. Second Edition. Pp. 950. Price 30s.

There are no essential differences between this edition and its predecessor which was reviewed in these pages on its appearance (1933, **56**, 348). There is a new chapter on the psychological manifestations of organic nervous diseases, but whether this picking out for separate treatment of a single integral component of a clinical syndrome is in principle sound, or in practice useful, may well be doubted.

It is perhaps unfortunate that Scherer's recent researches upon the modes of growth of the gliomas appeared too late for inclusion, for they render obsolete much of the laboured and arbitrary classification of these growths that has had too long a vogue, and they throw a valuable light upon the clinical behaviour of the gliomas, and upon the early clinical recognition of intracranial tumour. This early recognition, without which all the modern refinements of radiographical diagnosis of intracranial tumour have no possible *raison d'être*, might well have obtained a more generous consideration than the author has given it. After all it is by his trained senses that the observer first comes to suspect the presence of tumour, and every possible help and information should be given him in respect of this first step. Now that the diagnosis and treatment of intracranial tumour are coming more and more to be undertaken by those with no general neurological experience, and therefore with no sufficient capacity for differential neurological diagnosis, it is more than ever essential that first things should come first, and these are clinical and not radiological. The author gives but four pages to the general clinical recognition of tumour, but ten to accessory, i.e. radiographical, methods.

A fuller account of geniculate herpes, both in respect of its signs and symptoms, and in its relation to Bell's palsy would have been useful, while a descriptive and critical statement of the newly recognized lesion, rupture of the intervertebral disc, might with advantage have been given.

The illustrations are of unequal value. While there are numerous radiograms of the skull, there is but one—and that singularly inadequate—of the myopathies. In fact, the muscular atrophies which lend themselves so well to illustration are poorly represented.

The author has provided a comprehensive and orthodox account of nervous diseases, though possibly it may be criticized as too detailed for the "internist," while not altogether adapted for the professed neurologist.

Shell Shock in France 1914-1918. By C. S. MYERS. Cambridge University Press. 1940. Pp. 144. Price 4s. 6d.

It is difficult to know why this book has been written, or what useful purpose it might be considered to serve. In plan it is a melange of personal reminiscences, interspersed with vague references to "certain exceptional personal differences" which it would be "unwise and useless to mention," but which are nevertheless repeatedly mentioned—though never described—and of brief and inadequate clinical accounts of the cases of war neurosis seen by the author during the last war. The title of the book, which the author admits to be inaccurate, is as unfortunate as the book itself. Dr. Myers has scarcely done himself justice in it.

Diseases of the Nervous System. By F. M. R. WALSHE. Edinburgh: E. & S. Livingstone. 1940. Pp. 288. Price 12s. 6d.

An introduction to clinical neurology for students which may be also useful to general practitioners without special training in nervous diseases should satisfy two requirements, a presentation of diseases so that their nature and the localization of the lesions responsible for the disturbances of function may be deduced from clinical manifestations rather than by using isolated symptoms or groups of symptoms as means of diagnosis, and a selection of those subjects which require special emphasis for educational and practical ends. The author of this small volume has succeeded in these respects. Rarer and less important pathological disorders are neglected or referred to only cursorily while the commoner nervous affections are adequately described.

In the first 40 pages, the author discusses in considerable detail the nature and causation of symptoms and the principles of neurological diagnosis. He emphasizes the fact, so often lost sight of, that illness must be considered in terms of time as well as of space, that it is a process the story of which is being told not a static state, and consequently the present can be usefully considered only in relation to the past and to the possible future; in other words the natural history of each disease must be carefully studied. Being essentially a clinical presentation, morbid anatomy is allotted little space but on the whole is adequate. On the other hand, the sections on the treatment and management of the commoner disorders are lucid and practical.

Many of the chapters, as those on syphilis of the nervous system, epilepsy, circulatory disorders and others, are models of compression without loss of essentials or of clarity, and few fail to provide adequate clinical pictures. In future editions a fuller treatment of the symptomatology of disseminated sclerosis will be desirable, certain omissions should be rectified and some statements reconsidered. Not enough

weight, for instance, is given to the significance of gradually progressive and extending symptoms in the diagnosis of cerebral tumours, and the types of sensory disturbances by lesions at different levels deserve more space. Aphasia is a notoriously difficult subject to treat concisely; a short sketch on the evolution of speech would aid the student to understand more easily its dissolutions. It will not be generally agreed that motor apraxia results from affections of the frontal lobes, and that in chiasmal lesions vision always fails first in the periphery of the fields.

Its clear and incisive style and the essentially personal but objective attitude of the author contribute further to make it an excellent handbook for the student and practitioner.

Neurosyphilis. By C. Worster Drought. Modern Medicine Monographs. London: John Bale & Staples Limited. 1940. Pp. 241. Price 10s. 6d.

A modern and comprehensive account of neurosyphilis, written from the point of view of the clinical neurologist, is a welcome addition to medical literature. We may look in it for adequate clinical description and for an account of treatment not wholly dominated by serological criteria.

Possibly not all neurologists would share the author's sanguine views as to the influence of anti-syphilitic remedies upon the course of tabes dorsalis, as expressed in his statement that prognosis in this malady depends upon the stage at which it is first detected. It is perhaps disappointing in the course of a minutely detailed account of every form of medicinal treatment for tabes to find no more than the mere mention of Fraenkel's re-education exercises for tabetic ataxy. The neurologist may question, too, whether the non-syphilitic Argyll Robertson pupil is quite the commonplace the author implies.

These, however, are minor criticisms of a sound and valuable monograph. There is a useful bibliography and an excellent index.

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